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On the Relation between the Concentration of Total Protein and of Globulin in the Urine and the Pathogenesis of Certain Renal Lesions in Bright's Disease. SAM S. BLACKMAN, JR., WILLARD E. GOODWIN AND MARY V. BUELL. With the technical assistance of Mr. Irvin Yaffe and Mr. Irving Miller 397

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ON THE RELATION BETWEEN THE CONCENTRATION OF TOTAL PROTEIN AND OF GLOBULIN IN THE URINE AND THE PATHOGENESIS OF CERTAIN RENAL LESIONS IN BRIGHT'S DISEASE[1]

SAM S. BLACKMAN, JR., WILLARD E. GOODWIN AND MARY V. BUELL

With the technical assistance of MR. IRVIN YAFFE and MR. IRVING MILLER

From the Department of Pathology and the Department of Medicine of The Johns Hopkins University and The Johns Hopkins Hospital

Submitted for publication May 28, 1941

The following observations represent a study which is still in progress and was undertaken in order to investigate the role of haematuria, albuminuria and globulinuria in causing accumulation within glomeruli and tubules of certain hyaline material which is in part responsible for the progressive renal failure of many cases of Bright's disease. We wish here to review the literature concerned with albumin and globulin in the urine, to record the method used for the determination of urinary proteins, and to describe the first groups of cases we have studied.

The urinary proteins of some cases were determined at frequent intervals for long periods. The results show that in cases which recovered, and in others during periods when renal function remained stationary, the urine usually contained either a small amount of protein (less than 0.5 grams per cent), or, when larger concentrations of protein were present, only a small proportion of globulin (less than 35 per cent). The urine of cases which developed progressive renal failure more frequently contained a high concentration of protein (more than 0.5 grams per cent) of which a large proportion, 35 per cent or more, was more often found to be globulin; and in chronic cases the more often both total protein and globulin were found in high concentration the more rapid was the progress of renal insufficiency.

[1] Aided by a grant from the Rockefeller Foundation Fluid Research Fund of the School of Medicine of The Johns Hopkins University.

These observations suggest that some of the hyaline material found microscopically in glomeruli and tubules accumulated during periods when the glomerular filtrate contained a high concentration of plasma protein in which the proportion of globulin approached or exceeded that of normal plasma.

Terminology: The term globulin is not meant to indicate a specific protein. By globulin we mean that part of the plasma or urinary protein which has been shown to be precipitated by various salts, under standard conditions, including a mixture of primary and secondary potassium phosphate (1, 2, 4), sodium chloride, magnesium sulfate, anhydrous sodium sulfate, ammonium sulfate and sodium sulfite (3). This is the generally accepted meaning of the term, and it includes several fractions such as fibrinogen, and A, B, and Y globulin (4, 5).

REVIEW OF THE LITERATURE

Relatively few studies have been made of the globulin content of the urine in Bright's disease, and very few have been carried out for long periods. The results have usually been expressed in the form of the quotient derived from the determination of albumin and globulin. While several authors have pointed out that a low quotient signifies poor prognosis, no explanation for this has been offered.

As early as 1866 Lehmann of Copenhagen found globulin in urine which contained protein (6); and he was the first, according to Joachim (7) and Gross (8), to make this discovery. In 1874 Senator found the highest proportion of urinary globulin in acute nephritis and amyloid disease (9). He observed that the proportion of globulin did not depend on the total concentration of protein.

Between 1874 and 1927 a number of reports on the urinary proteins appeared in the literature, including the papers of Hammarsten (quoted by Huppert (10)), Hoffman (11), Lecorché and Talamon (12), Paton (13), Csatáry (14), Joachim (7), Gross (8), Strauss (15), Autenreith (16), and Kollert and Starlinger (17).

Hammarsten found globulin to vary from about 8 to 60 per cent of the total protein. Hoffmann concluded that the A/G quotient was dependent on the intensity of the disease, and found decreasing globulin in the urine as improvement took place. Lecorché and Talamon found increasing urinary globulin during relapses, and when 50 per cent or more of the protein was globulin the prognosis was poor.

Paton described studies of Douglas and Mackenzie. In the specimens examined globulin varied from 2.5 to 62 per cent of the total protein. Castáry expressed his results in the form of the A/G quotient. When one calculates the percentage of globulin it is found that in three cases of chronic haemorrhagic nephritis examined from 5 to 8 times each (Group IV), the globulin varied from 20 to 51 per cent of the total protein. In six cases of nephrotic nephritis (Group II) it varied from about 10 to 69 per cent, and in amyloidosis from about 14 to 61 per cent of the total protein. In a case of acute nephritis following scarlet fever, as recovery took place the urinary globulin fell from 78 to 13.5 per cent of the total protein. Joachim, Gross, Strauss, Autenreith, and Kollert and Starlinger all made few analyses. Autenreith agreed with Hoffmann, Lecorché and Talamon, and Csatáry that the A/G quotient of the urine was low in severe cases, and that a decreasing quotient (*i.e.* increasing globulin) was found during exacerbations.

In 1927 Hiller, McIntosh, and Van Slyke reported a series of twenty-nine cases of nephrosis and nephritis (18). The extreme range in the numerical value of the urinary A/G ratio of each case is given in a chart from which we have calculated the variations in the proportion of globulin. Thus, in the five cases of nephrosis globulin varied from about 4.5 to 22 per cent, and in acute nephritis (four cases) from about 6 to 40 per cent of the urinary protein. In the nineteen cases of chronic nephritis the globulin ranged between about 7 and 60 per cent of the total protein. In the one case of amyloidosis it varied from about 25 to 67 per cent of the protein in the urine.

In 1929 Geill reported that in his cases of nephrosis (nine analyses of two cases) globulin varied between 4 and 10 per cent of the protein. In two cases of nephrotic nephritis, examined ten and fifteen times respectively, it varied from 6 to 16 per cent. In seventeen cases of acute and chronic nephritis (two to eight analyses) the urinary globulin ranged between 4 and 35 per cent of the protein. From 11 to 65 per cent of the urinary protein was found to be globulin in five cases of amyloidosis (19).

In 1936 a monograph on proteins in the urine was published by Bing (20). He gave case reports of twenty-one patients in which the percentage of albumin in the urine was determined. In eighteen the urinary proteins were analyzed from 1 to 5 times. On this basis he

concludes that there is no difference in the percentage of albumin in the urine in the various forms of Bright's disease. This conclusion is probably due to the fact that few analyses were made of the urine of individual patients.

In Case 13 of Bing's series the high proportion of globulin in the urine is in contrast to his conclusion that "most of the values (for albumin) in all groups lie round about 80" (per cent of total protein) in both glomerulonephritis and nephrosis. In this case, an example of nephrotic nephritis, during a period of one year and nine months, eleven analyses of urinary proteins were made. The proportion of globulin varied between 38 and 48 per cent of the total protein and during this period the blood urea gradually rose from 56 to 100 mg. per cent.

Longsworth and MacInnes (21) and Leutscher (22) used the electrophoretic method of Tiselius in studying various properties of proteins in urine. Longsworth and MacInnes analyzed three specimens of nephrotic urine, two obtained from one patient, and a single specimen from another patient. Leutscher made one examination of each of three specimens of nephrotic urine.

Longsworth and MacInnes were not particularly concerned with the proportion of albumin and globulin, but from the figures given in their Table I it may be seen that in one case 16 per cent of the urinary protein was globulin, while in the other case globulin made up 32 per cent of the protein. In the three specimens analyzed by Leutscher globulin varied from 8 to 32 per cent of the total protein. Leutscher observed that globulin in the urine increased when the proportion of the serum globulin was very high.

During the course of recent studies primarily concerned with the albumin-globulin ratio of the blood serum, Melnick, Field, and Parnall determined the globulin content of nine samples of urine. On the basis of this small series they concluded that urinary protein is derived principally from the albumin fraction of blood serum (23).

In summary, most studies on this subject are based on few examinations of the urine of individual cases. Review of the literature shows, however, that in all forms of Bright's disease which have been investigated the proportion of globulin in the urine is variable and may be high at times. Little effort has been made to explain the relation

noticed between high urinary globulin and poor prognosis, and the relationship in other cases between small proportions of globulin in the urine and preservation of renal function despite persistent marked albuminuria; although it has been suggested that the proportion of globulin in urine may be one of the factors in the pathogenesis of coagulation and organisation of fibrin which takes place in glomeruli in many cases (24).

METHODS

1. *Collection of Urine:* Twenty-four hour specimens were collected into clean dry glass bottles containing about 10 ml. of toluene. In one case chloroform was used as preservative for some of the specimens, and it was not always possible to obtain complete twenty-four hour specimens. A portion of the specimen to be analyzed was filtered into a dry glass bottle to which toluene was added.

2. *Chemical Analyses:* In summary the method used consists of three determinations of nitrogen, (1) the total nitrogen of a specimen prepared as described above, (2) the non-protein nitrogen of a filtrate from which the total protein was precipitated by means of 20 per cent trichloroacetic acid, and (3) the albumin nitrogen plus non-protein nitrogen of a filtrate, hereafter to be spoken of as the globulin filtrate, from which the globulin was precipitated by means of a 4.05 molar solution of primary and secondary potassium phosphate. The protein nitrogen was calculated in gm. per cent[2] as the difference between the total nitrogen and the non-protein nitrogen; and the total protein calculated by multiplying the value for the protein nitrogen by 6.25. The albumin nitrogen was calculated as the difference between the nitrogen of the globulin filtrate, and the non-protein nitrogen.

The procedure to be described was used for many years in the chemical laboratory of the department of medicine of The Johns Hopkins Hospital for the analysis of both plasma and urinary proteins under the direction of Dr. W. A. Perlzweig. It combines the following advantages; no reagents containing nitrogen are used, the precipitates formed may be separated by filtration, the precipitation of the globulin may be carried out at room temperature, the analyses are made by the standard macro-Kjeldahl method, and the pH of the solutions is adequately controlled by the reagents without special adjustment.

3. *Technique:* (*a*) *Total nitrogen:* The nitrogen was determined by the macro-Kjeldahl method in accurately pipetted 5 ml. samples (or 10 ml. of a mixture of equal volumes of urine and distilled water). The ammonia of the distillate was collected in N/14 hydrochloric acid, and the excess acid titrated against N/14 sodium hydroxide. As indicator, a mixture of methyl red and methylene blue dissolved in 95 per cent alcohol was used.

[2] The expression "grams per cent" as used here and throughout this paper indicates grams per one-hundred cubic centimeters of urine or blood.

(*b*) *Non-Protein Nitrogen:* The total protein was precipitated from the urine by the addition of 15 ml. of 20 per cent trichloroacetic acid to 15 ml. of urine.[3] The mixture was filtered through No. 5 Whatman filter paper, and 10 ml. of the clear filtrate were analyzed for nitrogen.

(*c*) *Nitrogen of the globulin filtrate:* The globulin was precipitated by the addition of 15 ml. of 4.05 molar potassium phosphate solution to 15 ml. of urine. After standing for 2 hours in a stoppered flask the mixture was filtered repeatedly through No. 5 Whatman filter paper until a clear filtrate was obtained. The nitrogen was determined in 10 ml. of this filtrate.

4. *Calculations:* After calculating the total nitrogen (T.N.), the non-protein nitrogen (N.P.N.) and the nitrogen of the globulin filtrate (N.G.F.) in grams per cent, the following calculations of protein nitrogen (P.N.), albumin nitrogen (A.N.), total protein (T.P.), and A/G ratio were made:

T.N. − N.P.N.	P.N.
N.G.F. − N.P.N.	A.N.
P.N. × 6.25	T.P.
A.N./P.N.	per cent of A.N. in the T.N.
100 − A.N. per cent	per cent of globulin nitrogen in the total nitrogen

Limitations of the Method

In order to learn the accuracy and limitations of the method outlined above, a series of 10 specimens of urine was analyzed repeatedly (6 to 10 times each), each determination being performed in duplicate. The concentration of protein in the different specimens varied from 0.2 ± to 2.5 ± grams per cent.

This procedure is capable of determining the total nitrogen with an error of 1 per cent or less when suitable quantities of nitrogen are being determined. Since the values for protein nitrogen and albumin nitrogen are calculated as the differences between the total nitrogen and non-protein nitrogen, and between nitrogen of the globulin filtrate and non-protein nitrogen respectively, and since the values so obtained are relatively small numbers, the method is less accurate when the concentration of protein is small than when it is large.

In general, we have found that when the concentration of protein in the urine is between 0.4 and 0.7 grams per cent, the protein nitrogen, total protein, and the relative percentages of globulin may be determined with a reasonable degree of accuracy; that is, in a series of determinations, the average of any two will vary from the average of any other duplicate determinations by 5 to 10 per cent. When the protein concentration is greater, 0.7 grams per cent or more, the variation in the results of repeated duplicate analyses is smaller; and it may range from 1.5 to 5 per cent when the protein concentration is as high as 1 or more grams per cent (Table 1).

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[3] In the beginning of this work to 15 ml. of urine were added 5 ml. of water and 10 ml. of 20 per cent trichloroacetic acid.

As a result of these limitations it was not possible to determine accurately the relative per cent of globulin in specimens containing less than 0.4 grams per cent of total protein; and it must be borne in mind that in the following case reports

TABLE 1

ANALYSIS NO.	PROTEIN NITROGEN	ALBUMIN NITROGEN	TOTAL PROTEIN	RELATIVE GLOBULIN
		Urine no. 1		
	grams per cent	*grams per cent*	*grams per cent*	*per cent*
1	0.064	0.051	0.400	20
2	0.065	0.050	0.406	23
3	0.063	0.049	0.394	22
4	0.064	0.051	0.400	20
5	0.066	0.052	0.413	21
6	0.064	0.053	0.400	17
7	0.065	0.054	0.406	17
8	0.065	0.052	0.406	20
9	0.063	0.050	0.394	21
10	0.061	0.051	0.381	16
		Urine no. 2		
1	0.129	0.085	0.806	34
2	0.132	0.082	0.825	38
3	0.130	0.082	0.813	37
4	0.128	0.083	0.800	35
5	0.128	0.085	0.800	34
6	0.131	0.086	0.819	34
7	0.132	0.085	0.825	36
		Urine no. 3		
1	0.217	0.150	1.356	31
2	0.218	0.150	1.363	31
3	0.215	0.151	1.344	30
4	0.215	0.148	1.344	31
5	0.220	0.150	1.375	32
6	0.220	0.153	1.375	30
7	0.219	0.155	1.369	29
8	0.219	0.153	1.369	30
9	0.221	0.149	1.381	33
10	0.218	0.150	1.363	31

the values given for the relative percentage of total protein which is globulin do not necessarily represent precisely the absolute proportion of globulin. In any given instance, were the globulin determinations (the relative globulin per cent) repeated ten times in duplicate the average results of any pair of duplicates might

vary as much as 10 per cent when the concentration of total protein lies between 0.4 and 0.7 grams per cent. When the concentration is 0.7 grams per cent or more, however, the results obtained by repeated determinations of the globulin proportion would not vary more than 5 per cent.

The Relation between pH of Urine and the Precipitation of Protein

In most cases the pH of twenty-four hour specimens collected as described was found to lie between 6 and 8, and it did not vary significantly when kept under toluene for long periods of time. In nine of a series of ten specimens examined from four to five times each at intervals during one month the change in hydrogen-ion concentration was less than one pH unit. The pH of one specimen changed from 7.08 to 7.80 during the first three weeks, and from 7.80 to 8.12 in the following ten days.

TABLE 2

Effect of pH of Urine on Precipitation of Protein

Urine no. 1

pH	P.N.	A.N.	T.P.	R.G.
	grams per cent	*grams per cent*	*grams per cent*	*per cent*
4.7	0.184	0.088	1.150	52
5.4	0.178	0.091	1.113	48
9.0	0.178	0.094	1.113	47
10.0	0.176	0.098	1.100	44

Since there is but little change in the pH of urine preserved under toluene, and since most of the analyses were made within a week after the urine was excreted, we did not adjust all specimens to a constant pH, but preferred to mix the urine with the protein precipitants at or near the hydrogen-ion concentration of the urine as excreted. This procedure seemed desirable because it was found, as will be discussed presently, that when the pH of a given specimen was adjusted over a wide range (4.7 to 10) the differences in the analytical results which could be attributed to this variant were but slightly greater than those inherent in the method; more globulin being precipitated in the more acid specimens.

The slight effect of pH of the urine on the analytical results was demonstrated as follows. Four aliquots of the same twenty-four hour collection of urine were analyzed; without adjustment of pH, after adjustment to pH 4.7, the iso-electric point of serum albumin, to pH 5.4, the iso-electric point of serum globulin, and to pH 10. The determinations of pH were made by means of the glass electrode. The analyses at these four reactions were carried out, each in duplicate, as described above. As shown in Table 2, the variations in the results are slightly greater than those obtained when a number of analyses (10 in duplicate) are made

of urine at a constant pH, indicating that slightly more protein is precipitated in highly acid urine.

Effect of Time on Precipitation of Globulin by Phosphate Mixture

As outlined above in the section on technique, in order to precipitate the globulins, equal parts of urine and phosphate mixture were used. In order to test the effect of time on the completeness of precipitation of globulin by this method, samples of a given urine and phosphate mixture were mixed in equal parts, and after standing for two, four and six hours were filtered and the nitrogen of the filtrate was determined. As shown in Table 3 the difference between the percentage of globulin precipitated in two and six hours was within the limits of accuracy of the method.

TABLE 3

Effect of Time on Precipitation of Globulin

TIME	P.N.	A.N.	T.P.	R.G.
hours	*grams per cent*	*grams per cent*	*grams per cent*	*per cent*
2	0.088	0.071	0.550	19
4	0.084	0.068	0.525	19
6	0.084	0.066	0.525	21

THE CASES STUDIED

This study is based on a group of 42 cases, examples of acute haemorrhagic nephritis, lipoid nephrosis, subacute and chronic progressive nephritis with oedema. The cases have been divided into six groups. Individual case reports, including chemical analyses of the urine, are listed in the appendix. Twenty-three patients died, 21 were autopsied. Ten recovered completely. The disease persists in the remaining 9, although in 2 renal function is normal and there is only a trace of protein in the urine.

RESULTS

Group 1: Acute Nephritis. Proteinuria Usually of Low Concentration

Eight cases of acute haemorrhagic nephritis and one "toxaemia" of pregnancy are included here. The acute nephritis was characterized by gross haematuria and low concentrations of protein in the urine (0.019 to 0.444 grams per cent). Five of the patients recovered. In another (No. 6) the urine contained a few red blood cells micro-

scopically, and very small amounts of protein (0.040 to 0.050 grams per cent) four and a half years after the onset, but the serum N.P.N. and urea clearance were normal (92 and 100 per cent of normal maximum).

Two cases of acute nephritis died (Nos. 7 and 8). In these, also, there were small amounts of protein in the urine, less than 0.5 grams per cent. The kidneys showed the lesions of acute diffuse glomerular nephritis without, however, appreciable amounts of exudate in the glomeruli and tubules.

In Case 9 of this group, an obese woman of 39, there was massive proteinuria, anasarca, pregnancy, and hypertension. Generalized oedema was present for a few days, oedema of the ankles for 2 months. It seems fair to assume, therefore, that the marked proteinuria found on admission to the hospital had existed for only a short time. During 3 days before delivery was induced the concentration of protein in the urine varied between 0.994 and 1.319 grams per cent, the proportion of globulin from 35 to 52 per cent of the total protein. After delivery, proteinuria dropped to 0.325 grams per cent within a few hours, and during the following 11 days gradually fell to 0.075 grams per cent. A few days later the urea clearance was 83 and 90 per cent of normal maximum.

In summary, the urine of 8 cases of acute haemorrhagic nephritis and of a single case of "toxaemia" of pregnancy was examined frequently during the most intense periods of the disease in nearly every case. The concentration of protein in the urine was usually low in acute nephritis, and was high for a short time in the other case. The proportion of globulin in the urine was high in all of these cases whenever it could be determined. The patients recovered, or showed no renal impairment following a short period of marked proteinuria and globulinuria (Case 9), or the kidneys were found to contain no appreciable collection of coagulated exudate.

It may be concluded from these cases that proteinuria of low or high concentration and of short duration, even accompanied by gross haematuria and by high proportions of globulin in the urine, may occur without the accumulation of exudate in the kidneys sufficient to cause appreciable impairment of renal function.

Group 2: Acute Nephritis. Proteinuria and Globulinuria of High Concentration

In the second group 2 examples of fatal haemorrhagic nephritis are included. They showed gross haematuria and massive proteinuria (0.838 to 1.762 grams per cent); and from 40 to 50 per cent of the total protein in the urine was globulin. Both patients died in uraemia. One was autopsied. The glomerular lesions were like those in the autopsied cases of Group 1. In addition, there were clots of fibrinous exudate in many Bowman's spaces, in clefts between tufts of capillaries, and in tubules. In such cases the presence in the glomerular filtrate of urine in which total protein and globulin are present in high concentration seems to be one of the factors responsible for coagulation of fibrinous exudate within glomeruli and tubules.

Group 3: Lipoid Nephrosis and Nephrotic Nephritis. Proteinuria Usually Accompanied by Globulinuria of Low Concentration and by Normal or Nearly Stationary Renal Function

Group 3 includes ten cases characterized by chronic and at times massive proteinuria, oedema, lipaemia, and by the irregular occurrence of microscopical haematuria. Gross haematuria was observed in three cases. The urinary proteins were frequently analyzed during periods which varied from 1 to 22 months. The proportion of globulin was rarely as high as 35 per cent of the total protein, and was usually much lower. The patients recovered completely (Nos. 1, 2, 3, 4, 5 and 7), or almost completely (Nos. 6 and 8), or showed little decrease in renal function during the periods of study (Nos. 9 and 10).

Eight cases were examples of nephrosis and nephrotic nephritis without chronic hypertension, occurring in children and young adults. The duration of the disease varied from 7 months to $4\frac{1}{2}$ years. Microscopical haematuria occurred at times in all 8, and gross haematuria was observed in 2 (Nos. 7 and 8). The urine of 6 became normal, and all signs and symptoms of the disease disappeared, without residual renal impairment of hypertension. The urine of 2 (Nos. 6 and 8) contained traces of protein (0.031 to 0.056 grams per cent) $2\frac{1}{2}$ and 4 years respectively after the onset; and the urea clearance and blood pressure were normal.

The other cases in this group (Nos. 9 and 10) are examples of chronic nephritis with renal function impaired when the patients were first examined. They are characterized by proteinuria and microscopical haematuria, variable oedema, and by blood pressure which is normal at times and is frequently elevated. Gross haematuria occurred early in the disease in 1 case. The duration of the nephritis, which still persists, is 2 and 2½ years respectively. The urine was analyzed 84 times in 22 months. The combination of high proteinuria and globulinuria was rarely found and there has been little decrease in urea clearance during this time.

These cases show that chronic proteinuria, frequently of high concentration, usually low in the proportion of globulin, accompanied by microscopical haematuria and occasionally by gross haematuria, may be followed by complete recovery with normal renal function and blood pressure.

Two cases, studied first when slight to moderate hypertension and impaired renal function had already developed, show that in the absence of increasing hypertension, little change in renal function may occur during long periods of moderate to marked proteinuria and little globulinuria. The observations on the whole Group suggest that in the presence of proteinuria and haematuria, impairment of renal function due to the collection of hyaline exudate in glomeruli and tubules does not tend to develop rapidly so long as the concentration of both total protein and of globulin in the urine is not high.

Group 4: Nephrotic Nephritis. Proteinuria and Globulinuria of High Concentration, Accompanied by Progressive Renal Failure

The 10 cases in Group 4 were especially characterized by the presence of high proportions of globulin in urine which also contained total protein in high concentration, and by the relatively rapid development of renal insufficiency. In 8 the duration of the disease varied from 9 weeks to about 2 years. One patient lived 3 years. The remaining patient could be studied for only the first 5 months of the disease. During this time the urea clearance fell to 22 per cent of normal standard. Nine of the patients died and were autopsied. The signs and symptoms in this group consisted of marked proteinuria and globulinuria, oedema, lipaemia and microscopical haematuria.

Gross haematuria was observed in 1 case. Hypertension was present at times in 8, but the blood pressure was never above normal in 2 cases (Nos. 4 and 8).

The urine of 3 cases was analyzed only 1 or 2 times. The proportion of globulin in these specimens varied from 42 to 50 per cent of the total protein. In 6 cases the urine was analyzed from 4 to 14 times. A high proportion of globulin was often found, varying from 35 to 64 per cent of the total protein. The urine of Case 9 was examined 55 times in 13 months. The total protein was nearly always above 1 per cent, decreasing during the last 4 months; and the globulin was usually 35 per cent or more of the total protein.

Three cases in this Group are of particular interest. The duration of the disease was only about 9 weeks in Case 4. Studied during the last 5 weeks of the disease the urea clearance fell from 29 and 32 per cent to 0.52 and 1.23 per cent of normal standard. During 2 weeks of this period the urine was analyzed 4 times. The total protein varied between 0.632 and 2.620 grams per cent, and the proportion of globulin from 58 to 64 per cent of the protein. The plasma-protein A/G ratio fell to 19/81. The blood pressure was never above normal, and nothing was found to account for renal failure except slight accumulation of exudate about glomerular capillaries and obstruction of many tubules by exudate.

In Case 7 also renal insufficiency developed during a period when the urine contained total protein and globulin in high concentration. The patient was studied for two months in 1935. The urea clearance was 62 per cent of normal maximum and 71 per cent of normal standard. The serum N.P.N. and phthalein excretion were normal. The urinary proteins were analyzed 6 times during this period. The concentration of protein was high (0.481 to 1.350 grams per cent), but the highest proportion of globulin was 18 per cent of the total protein. During the following 13 months the protein concentration in urine varied from 0.587 to 1.825 per cent and on 5 of 8 analyses the proportion of globulin varied from 35 to 50 per cent. In this period the patient developed renal insufficiency and died.

When Case 9 was first studied, about 9 months after proteinuria was discovered, the urea clearance was 67 and 46 per cent of normal standard. During the following 13 months the urine was examined

at weekly intervals. The protein concentration was nearly always above 1 per cent. The proportion of globulin was usually above 30 per cent, often between 35 and 50 per cent of the total protein. The urea clearance fell progressively to 3 per cent of normal standard, and the patient died in uraemia.

The cases in this Group suggest that high concentration of both total protein and globulin in the urine was one of the conditions necessary for coagulation of hyaline exudate found microscopically in glomeruli and tubules; and it seems evident that the presence of these hyaline materials was one of the factors in the pathogenesis of rapid renal failure.

Group 5: Chronic Proteinuria, Occasional High Globulinuria, and Very Slow Renal Failure

In Group 5, 4 cases are included, 3 of which have in common two features; (a) the progressive increase of renal impairment at a very slow rate over a long period, and (b) the *occasional* occurrence of the combination of proteinuria of high concentration plus a high proportion of globulin.

In the first case, a girl of 15 years when first examined, studies were begun a month after the onset of symptoms. The urea clearance was 26 per cent of normal standard and 30 per cent of normal maximum. Ten analyses were made of the urinary protein. The total protein varied between 0.244 and 0.588 grams per cent. A concentration of protein of 0.5 grams per cent or more, together with globulin content of 35 per cent or more, was found on only 2 of 10 analyses. Four years later the urine was examined twice at weekly intervals. It contained small amounts, 0.163 and 0.200 grams per cent of protein, and the urea clearance was 6.7 and 16 per cent of normal maximum.

The second case was a child of 7. During a period of 2 years the urinary proteins were analyzed 23 times, beginning 9 months after the onset of symptoms and ending a year and 7 months before death. On four occasions during this time the urine contained a high concentration of both total protein and globulin. The child finally died in uraemia $5\frac{1}{2}$ years after the onset. The kidneys contained considerable quantities of hyaline material in the glomeruli, little in the tubules.

In Case 3 the duration of the disease was more than $9\frac{1}{2}$ years. The

patient was a girl 14 years old at the onset in 1930. The urinary proteins were analyzed 41 times in 13 months, beginning about 5 years after the onset and ending 3½ years before death. Although the concentration of protein in the urine was nearly always more than 0.5 grams per cent, a proportion of globulin around 35 per cent was found only twice. The highest urea clearance in 1930 was 70 and 55 per cent of normal maximum, and in 1936 it was about the same. No further studies were made until 1939 when the urea clearance was found to be 11 and 10 per cent of normal standard. The patient died 14 months later. An autopsy was not performed.

The fourth case in this Group is included here for convenience. The patient was an infant presenting the signs and symptoms of lipoid nephrosis. The disease terminated with pneumococcal septicaemia and peritonitis about 2 years after the onset. Four analyses of urinary proteins were made during the last 16 days of the disease. The concentration of protein in the urine was always above 1 gram per cent and on one occasion 44 per cent of the protein was globulin. Microscopical sections of the kidneys showed the changes usually found in lipoid nephrosis (27), and in addition there were a few very small focal collections of hyaline material coagulated about glomeruli capillaries and in clumps 4 to 24μ in diameter lying between loops of capillaries.

Group 6: Effect of Advanced Renal Failure on Proteinuria

Seven cases are included here. The urinary proteins were analyzed during the terminal stages of renal insufficiency. All of the cases were autopsied. Two were examples of chronic hypertension and arterio- and arteriolosclerotic nephritis. In the others renal insufficiency was due to chronic pyelonephritis and chronic glomerulonephritis, alone or in combination.

The urine of individual cases was analyzed from 3 to 24 times during periods varying from 1 week to 9 months. A total of 61 analyses was made. A high concentration of both total protein and globulin was found in only one specimen. These cases show that renal insufficiency per se is not the cause of high concentrations of total protein and globulin in the urine. This is in accord with the clinical observation that, as expressed by Fishberg (28), in the late stages of long standing

chronic glomerulonephritis, "albuminuria" is often slight and may even be absent at times.

THE RENAL LESIONS

The kidneys of the autopsied cases are described in the appendix. No two cases are exactly alike in the degree of development of lesions, and even in a given case, various glomeruli are unequally altered. It is well known that the development of renal insufficiency is influenced by lesions in many parts of the kidney, such as the collection of materials within glomeruli and tubules, alterations in renal epithelium, scarring of the interstitial tissue, and by narrowing of blood vessels. We wish at this point to describe and discuss the fibrin and hyaline materials found within glomeruli and tubules of the autopsied cases of this series, and are not concerned with other lesions.

In the subacute and chronic cases, the glomeruli and tubules contain varying amounts of hyaline material, and it is possible to identify two morphological varieties in the glomeruli. Hyaline crescents represent one variety. They are derived, as is well known, from coagulated exudate, chiefly fibrin, proliferating epithelium which becomes necrotic and hyaline, and connective tissue. In the end, hyaline crescents usually have a somewhat stratified, fibrillary structure, and are not as compact, homogeneous, and highly refractive as the other variety of hyaline material.

Corresponding in appearance to the hyaline crescents in Bowman's spaces there is a similar fibrillary hyaline material within the glomeruli of some of the cases. Lying within the tufts one finds this material together with varying numbers of nuclei. MacCallum has shown that it contains connective tissue, and is intercapillary in position (29). It is not composed entirely of connective tissue, however, and it is likely, as in the case of crescents, that necrotic epithelium is incorporated in the hyaline mass. In some of these cases one may easily find proliferating epithelial cells between capillary loops, others with swollen cytoplasm transformed into "colloid" drops, and others which are necrotic.

It is difficult to determine whether or not this hyaline material and scar tissue is derived from organisation of fibrin or other coagula. We can only say that in the present series, as well as in many other

examples of nephritis examined by means of fibrin stains and other stains, it has been impossible to identify with certainty the characteristic threads of fibrin in this intercapillary location. On the other hand, fresh and older compact masses of fibrin can be identified within tubules, in Bowman's spaces, and in the clefts between tufts of capillaries. Finally, scattered in some of the fibrillary hyaline glomeruli, we have found masses of the second variety of hyaline material.

This second variety is present in glomeruli and tubules of all subacute and chronic cases in the present series. It is abundant in some and scanty in others, but is not peculiar to this series. The material looks different in several respects from the more fibrillary hyaline glomeruli and crescents.

It resembles and stains like coagulated and inspissated blood serum. It seems clearly to be something which escapes through glomerular capillaries and precipitates about them and in tubules where some of it may remain. In the glomeruli its location is peculiar, and it is found almost exclusively between the capillaries, surrounding them, and sometimes infiltrating their walls. In some cases even the walls of hilar arterioles are infiltrated by it. Rarely small masses may be found within Bowman's spaces, and more often within hyaline crescents. Large masses, however, comparable to crescent-shaped clots of fibrin, have not been found in Bowman's spaces of any cases in this series or in many others we have examined.

This variety of hyaline material stains with eosin, looks homogeneous and smooth, and is highly refractive. When examined under the oil immersion lens it is found to be arranged in the form of irregularly shaped, confluent masses. The glomerular capillaries and variable numbers of intercapillary nuclei and fibers are imbedded in it.

The material may collect diffusely about all of the capillaries, or it may be found in small foci about single capillary loops of a few glomeruli. In Case 3 of Group 4, the material infiltrated and collected about all of the capillaries to a moderate extent, the disease having lasted something over a year. In Case 2 of Group 5, the duration being over 5 years, the glomeruli are enlarged and contain more of the hyaline material. In Case 2 of Group 4, the disease was of short duration (8 months), but the urine, examined once, contained enormous amounts of protein (3.480 grams per cent) and a high proportion of

globulin (42 per cent). The glomeruli are very greatly enlarged due to the collection of this hyaline exudate about the capillaries. In Case 4 of Group 5, an infant with nephrosis, the material is present about occasional isolated capillary loops in scattered glomeruli. This case is of interest in illustrating that this lesion may develop in foci, not necessarily as a diffuse process, and because the proportion of globulin was high in the urinary protein on one of four examinations, suggesting that the precipitation of hyaline material occurred during periods of high globulinuria.

In Case 4 of Group 4, in which there was no elevation of blood pressure and the disease lasted only 9 weeks, little of the exudate collected in the glomeruli. Many tubules, however, are distended and obstructed by dense hyaline masses which caused pressure atrophy of tubular epithelium. The material in these tubules resembles precisely that found in large amounts in glomeruli of other cases.

Further characteristics of this material are that it somewhat resembles but gives negative reactions for amyloid. It is acid fast (carbol fuchsin) both in glomeruli and tubules, and this suggests that it contains lipoids. Frozen sections give positive results for fat (Scharlach R) in some areas of the hyaline material. One can also find "Maltese crosses" of cholesterol esters in it in glomeruli of some cases, but most of the lipoid-containing masses are not doubly refractive. When stained with phosphotungstic acid hematoxylin (Zenker fixation) most of the material is orange colored. In some cases a little of it, like fresh fibrin, is blue or purplish.

In the present series of subacute and chronic cases many tubules in some, few in others, contains the hyaline material, identical morphologically and in staining properties with that in the glomeruli. The fact that it causes dilatation and obstruction of tubules, and pressure atrophy of the epithelium is evidence that it remains within the tubules for at least a considerable period of time. Other casts in variable numbers are also found in tubules of these cases. Some are composed of fresh fibrin, and some of older, compact, granular and laminated fibrin. Some tubules contain blood and there are leucocytes in some. But the tubules which contain blood, leucocytes, and fresh fibrin rarely show pressure atrophy of the epithelium, unless the hyaline material is also present.

We have made iron stains of the kidneys of all of these cases and of others in an attempt to find evidence of retained red blood cells or blood pigment in the crescents and in the other hyaline material. In none of the cases, however, have we found haemosiderin in the glomeruli or within the lumina of tubules. This suggests that the red blood cells which escape play little part in causing the accumulation within the kidney of scar tissue and of the other hyaline material.

DISCUSSION

These analyses show that in the forms of Bright's disease which we have investigated, acute haemorrhagic nephritis, lipoid nephrosis, and chronic nephrotic nephritis, high proportions of globulin are excreted in the urine at times. The conclusions of several recent investigators that most of the urinary protein is composed of albumin, are apparently due to the fact that in the majority of the cases studied few analyses were made of the urine of each individual patient. In order to observe the variations which occur in the concentration of total protein and of globulin in the urine, it is necessary to make numerous analyses.

There is no difficulty in recognizing clots of fibrin when they occur in glomeruli and tubules of the kidney, and it is well known that fibrinogen, the precursor of fibrin, is one of the globulins of the blood plasma. The following evidence suggests that the hyaline masses, designated above as the second variety of hyaline material, also represent coagulated plasma protein rich in globulins.

The material collects especially in kidneys of patients whose urine frequently contains total protein and globulin in high concentration, and it does not tend to collect in the kidneys if the urine contains total protein in high concentration and globulin in low concentraton. Microscopically it looks and stains like inspissated blood serum. It resembles what is generally recognized as serous exudate in other tissues, and the hyaline material in old thrombi. There seems to be little other source of origin for the material, especially since it is readily distinguishable from necrotic renal epithelium. The evidence suggests that globulins are especially concerned in the formation of this material, and it may be that varying proportions of different globulins collect in different cases. It may be, too, that the material in the

glomeruli and tubules represents mixtures of different protein fractions, not necessarily the same in the two locations.

The possibility suggests itself that the presence of this hyaline material in the kidneys may be the cause of escape in the urine of total protein and globulin in high concentration. The following evidence speaks against this possibility. The cause of proteins in the urine in high concentration is evidently related to whatever factors determine the permeability of glomerular capillaries to plasma proteins, and it is well known that in the most advanced stages of renal insufficiency, when scar tissue and hyaline materials are most abundant in the glomeruli, proteinuria diminishes. The seven cases in Group 6, studied in the terminal stages of chronic renal failure, show plainly that proteinuria and globulinuria of high concentration are not caused either by renal failure *per se*, or by the visible anatomical lesions, including the various forms of hyalinized glomeruli responsible for chronic renal failure. Furthermore, the glomeruli are in many cases permeable to high concentrations of plasma proteins in the early stages of nephritis, before appreciable collection of fibrin or hyaline material has occurred, at a time when it is difficult to see microscopical changes which can be identified as the cause of capillary permeability. This evidence suggests that capillary permeability to plasma proteins represents an injury which is difficult to see microscopically, and that in the presence of chronic permeability of high degree, some of the proteins which escape gradually precipitate in glomeruli and tubules in the form of hyaline material.

We have assumed that the presence of hyaline materials in the glomeruli and tubules interferes with renal function, and may briefly summarize here the evidence for this view. In glomeruli the material is intercapillary in position. It may infiltrate the walls of capillaries and so make them thicker than normal (Plate 2, Fig. 1). This would interfere with normal filtration depending on the number of capillaries affected and the degree of thickening. The material also collects in the form of masses which become so large that the capillaries are stenosed or occluded by pressure from without (Plate 2, Figs. 3 and 4). Perfusion of the kidneys shows that many of the capillaries are still patent and can be opened, and that they are not occupied by new endothelial cells or coagula. But there is no doubt that many of

them are more or less completely surrounded by solid masses of the hyaline material, and there is little reason to doubt that this interferes with normal filtration (Plate 4, Figs. 3 and 4).

In tubules the hyaline material causes obstruction, and interferes with normal renal function. The material may be found in few or many tubules. The degree and duration of obstruction may be judged to some extent by the degree of dilatation of the tubules and by the extent of flattening of the epithelium. In some cases in the series many tubules show extreme obstruction and dilatation, and on one case (Plate 4, Figs. 1 and 2) renal insufficiency was probably caused in large measure by tubular obstruction, for only slight changes could be found in the glomeruli.

It is not unlikely that the degree of tubular obstruction may vary from time to time. During periods of diminished proteinuria more of the hyaline material may escape as casts in the urine than is precipitated in tubules, and during periods of increased proteinuria and globulinuria more numerous tubules may become obstructed. Whether or not the material, once precipitated in its intercapillary position in the glomeruli, is capable thereafter of escape in the urine, seems doubtful.

There appears, then, to be little reason to doubt that the hyaline material in glomeruli and tubules reduces renal function, and there is even evidence that obstruction of many tubules by it may be reflected in low urea clearance values (Group 4, Case 4). We wish to state clearly, however, that in some of these cases the presence of hyaline materials represents only one of the factors concerned in causing renal failure. The extent to which this particular factor was concerned is different in each case, and in some cases it probably played a minor role.

It is evident that in every case of Bright's disease the greater part of the protein in the glomerular filtrate escapes daily in the urine; and the factors which are concerned in determining the nature, location, and quantity of protein that may precipitate within the glomeruli and tubules are probably numerous and complex.

From the cases in this series it may be said that in acute haemorrhagic nephritis fibrinous exudate may collect rapidly, within a few days, in the Bowman's spaces of many glomeruli and in some tubules.

Little of the other hyaline material was found either in glomeruli or tubules of acute cases. Fibrinous exudate in the glomeruli was never recognized in the intercapillary spaces, only within the epithelial lined spaces of Bowman. It was found only in the cases in which both total protein and globulin were present in the urine in high concentration. Fibrin clots in the tubules were never found to be very numerous, either in the acute or chronic cases. The urine of most cases of acute nephritis in the series contained protein in low concentration, despite gross haematuria, and the patients recovered. Such evidence suggests that the presence of a high concentration of globulins in urine which also contains total protein in high concentration, is significantly concerned in the clotting of fibrin within the glomeruli and tubules.

In many of the subacute and chronic cases small quantities of fresh fibrin were found in glomeruli and tubules, and there was evidence of old organized fibrin in the form of crescents. Much more abundant in some of the cases, however, was the accumulation of a different hyaline material in glomeruli and tubules. This substance was for the most part beneath the visceral layer of epithelium in the glomeruli, intercapillary in position. In some cases the walls of capillaries and arterioles were infiltrated and thickened by it. Lipoids could be stained in some of the hyaline exudate in the tubules and more especially in the glomeruli of cases in which lipaemia occurred during life. These studies have little bearing on, and there is scarcely any information available concerning the precise nature of the chemical or physicochemical processes responsible for precipitation within the kidneys of proteins other than fibrinogen. It is perhaps of some interest in this connection, however, that, as is well known, the globulins are more readily precipitated by various salts than the albumins.

The cases of this series do suggest two factors of particular significance in causing the collection of these hyaline exudates, namely the duration and the concentration of both total proteinuria and globulinuria. The more frequently high concentrations of total protein and globulin were found in the urine, the more rapidly renal insufficiency progressed and the more abundant was the hyaline exudate in the kidneys of the autopsied cases. The cases which recovered, or progressed very slowly, or at autopsy showed little fibrinous and hyaline exudate in the kidneys, were characterized either by proteinuria of low

concentration, or by marked proteinuria and low globulinuria, or by the infrequent occurrence or short duration of both proteinuria and globulinuria of high concentration.

Even when proteinuria and globulinuria of high concentration exist together the hyaline material collects in the kidney gradually. It appears, too, that the conditions most favorable for its precipitation in the glomeruli and tubules are not necessarily the same. These facts are well illustrated by a case of nephrotic nephritis 9 weeks in duration (Group 4, Case 4). During this relatively short period little exudate collected in the glomeruli, but most of the tubules in the cortex were obstructed and extremely distended by large masses of hyaline coagula. The urine contained protein varying from 0.631 to 2.019 grams per cent, and the proportion of globulin ranged from 58 to 64 per cent of the total protein.

The urine of the patients with lipoid nephrosis was characterized by the infrequent presence of both total protein and globulin in high concentration. This is probably one of the reasons why such cases show little evidence of protein coagula and scars in the kidneys. But it is perhaps more significant that in this disease proteinuria may disappear completely and permanently. Total proteinuria and globulinuria of high concentration do occur together at times in nephrosis, and if the proteinuria should fail to disappear, there is reason to believe that renal insufficiency would eventually develop, depending partly on the frequency of action of those factors which cause total proteinuria and globulinuria of high concentration to occur together.

We wish to point out again, as already suggested (24, 27), that there is as much reason to consider the red cells, leucocytes and plasma protein in the urine of "nephrosis" to be an inflammatory exudate as in "nephritis." Chemical analyses show that in cases which everyone would agree are examples of chronic "nephritis," the character and quantity of proteins in the urine are at times the same as those found in the urine of patients with nephrosis. In what we call chronic nephritis the proteinuria persists relentlessly and total protein and globulin occur together in high concentration more frequently than in nephrosis. The persistent idea that nephrosis is a so-called degenerative disease, in contrast in this respect to nephritis, an inflammatory

disease (30), disregards all evidence except the fact that in nephritis certain portions of the inflammatory exudate collect in the kidney and are visible under the microscope. Whether or not in any case some of the exudate coagulates and remains fixed within the kidney to interfere with renal function is apparently related to the duration of proteinuria and the concentration in which the various proteins are excreted.

These cases suggest that in Bright's disease frequent determinations of the concentration of proteins in the urine afford an indication of the intensity of the disease process. In other words, such information concerning the urinary proteins seems to indicate first the degree of damage (difficult to see microscopically) which is responsible for glomerular capillary permeability to plasma proteins, secondly something of the rate and quantity of collection within the kidney of protein coagula, and thirdly the rate and quantity of collection in the glomeruli of those other hyaline and cellular materials which may or may not be stimulated to form as a result of clots or coagula of protein.

The examination of the urine charts of the cases in this series, together with microscopical study of the kidneys and the history of each case, leads to the conclusion that haematuria alone is perhaps not as indicative of poor prognosis in the chronic nephrotic forms of Bright's disease as it is generally considered to be. In Case 3 of Group 5, for example, a case of chronic nephrotic nephritis, 9½ years in duration, gross haematuria occurred on several occasions, and red blood cells were found microscopically on 291 of 320 examinations. All of the cases in Group 3 that recovered exhibited microscopical haematuria at times. In one of these (Case 7) gross haematuria occurred at the onset, and subsequently during a period of 3 months from 2 to 75 red blood cells per high-power-field were found whenever the urine was examined microscopically (105 examinations). In another case in this Group (No. 8), although gross haematuria occurred at the onset, and despite the microscopical haematuria of 1 to 10 cells per high power field on 185 of 215 examinations, 4 years after the onset the urea clearance was normal and the urine contained only a small amount of protein. In a third case (No. 6) microscopical haematuria of 1 to 20 cells per high-power-field was found on 80 of 117 examinations. Four and a half years from the onset, however, the urea clearance and blood

pressure were normal, and there was only a trace of protein in the urine.

Further, regarding haematuria, it was neither an index of the concentration of total protein or of globulin in the urine of these cases. The cases in Group 4, in which renal failure progressed most rapidly, and in which total protein and globulin were present in the urine in the highest concentration, and, in the cases which were autopsied, precipitated protein was most abundant in the kidneys, exhibited during life less haematuria (Nos. 4, 5, 8, and 9) than others in which the disease lasted far longer and haematuria was more pronounced (Nos. 1, 2, and 3, Group 5). Furthermore, haematuria was no more marked in some of these fatal cases in Group 4 with very marked proteinuria and globulinuria than in some of the cases of Group 3 which recovered and showed little proteinuria, or, if marked proteinuria, little globulinuria (Nos. 5, 6, and 7, Group 3).

Finally, the fact that most cases of acute haemorrhagic nephritis recover, and that in chronic cases one can find no microscopical evidence that red blood cells or their pigmented products remain fixed within the glomeruli or tubules to take part in the formation of hyaline coagula and scar tissue also suggests that haematuria *per se* is relatively insignificant in the pathogenesis of the permanent lesions which cause renal insufficiency. This is consistent with the well known fact that benign "albuminuria," whether orthostatic or not, may be accompanied by microscopical haematuria (31).

SUMMARY AND CONCLUSIONS

A review of the literature concerning the relative proportions of albumin and globulin in the urine in Bright's disease reveals two conflicting opinions. Some investigators have concluded that in general the urinary protein consists chiefly of plasma albumin. This conclusion has generally been drawn from analyses of urinary proteins made during short periods of the disease of individual patients. Others have shown that at times high proportions of globulin do appear in the urine. It has been pointed out by several students of the subject that a high proportion of globulin in the urine may be indicative of poor prognosis.

For several years we have studied the relationship in forty-two exam-

ples of Bright's disease between the concentration of total protein and globulin in the urine and the development of renal insufficiency. The method used for analysis of urinary proteins is described, and its limitations in our hands are defined. In more than half of the cases frequent analyses of the urinary proteins were made, 24-hour specimens being obtained at about weekly intervals during periods ranging from 2 months to 2 years. Histological examinations of the kidneys were made in 21 of the cases.

The results indicate that the element of renal insufficiency which is due to the collection of fibrin, hyaline and organized exudate within the kidney develops during periods when the concentration of total protein and of globulin are both high in the urine, and that not only the fibrin but also the more abundant hyaline materials may represent precipitated globulins. The studies suggest further that two factors are of especial significance in causing the protein exudates to collect within the kidney, namely the concentration and duration of total proteinuria and globulinuria. The relation between these factors and the presence or absence of exudate in the kidneys of the cases investigated may be summed up in the following manner.

Most of the cases of acute haemorrhagic nephritis exhibited proteinuria of low concentration, and recovery occurred. Cases of this character which were fatal showed little or no fibrinous or hyaline exudate in the kidneys. Fatal cases of acute nephritis in which proteinuria and globulinuria occurred in high concentration showed that considerable quantities of fibrin may collect in the kidneys within a few days time. In these and in other cases whenever fibrin was found in the glomeruli it was always within Bowman's epithelial lined spaces.

In the cases of chronic nephrotic nephritis some fibrin was found in the usual position, but much more abundant was a different hyaline coagulum in glomeruli and tubules. This material was found to collect in glomeruli almost exclusively in the walls and between the loops of individual capillaries. In this group of cases renal failure progressed at a rapid or slow rate, and the hyaline exudate in the kidneys of the autopsied cases was more or less abundant, depending upon whether or not the urine frequently or seldom contained total protein and globulin in high concentration.

The cases of lipoid nephrosis nearly all recovered. The concentration of total protein in the urine was frequently high, but the proportion of globulin was usually low. It is probable that the maintenance of normal glomerular function in lipoid nephrosis, the absence of appreciable numbers of hyalinized glomeruli, and the scarcity of tubules obstructed by protein coagula are all related to the fact that globulin is usually excreted in the urine in low concentration.

Some cases in the series indicate that the factors leading to precipitation of protein exudate in glomeruli are not entirely the same as those which may tend to cause precipitation within tubules. It seems likely that one of the differences may depend on the increased concentration of protein and salts in the tubules due to reabsorption of water by the epithelium, so long as the cells are functioning.

No correlation was apparent in these cases between the degree of haematuria and the concentration of either total protein or of globulin in the urine. This is probably due to the fact that haematuria is the result of bleeding from relatively few widely separated glomerular capillaries, while proteinuria is probably a more constant and diffuse phenomenon. We were unable to find histological evidence that red blood cells or their pigmentary products took part in the formation of the permanent protein coagula or scars within the kidneys of any of the cases.

A group of cases studied in the terminal stages of renal failure shows that proteinuria and globulinuria of high concentration are not caused either by renal failure *per se*, or by the visible anatomical lesions responsible for chronic renal failure.

Finally, it seems worthwhile to suggest that in many cases of Bright's disease it might be possible to prevent or retard the accumulation of protein coagula in glomeruli and tubules by decreasing the concentration of protein in the glomerular filtrate. This might be accomplished by increasing the ingestion of fluids.

We wish to thank those who have helped with this work, and are especially indebted to Dr. Warfield T. Longcope, Dr. Edwards A. Park, Dr. Francis F. Schwentker, and to many members of the medical, pediatric, and nursing staffs of The Johns Hopkins Hospital, the Sinai Hospital and the Sydenham Hospital of Baltimore.

APPENDIX

GROUP 1

Case 1. C. D., C. M. 5½ years old. *Diagnosis:* Acute haemorrhagic nephritis. *History:* March 20, 1935, oedema was noticed. Examinations showed proteinuria, haematuria, oedema and hypertension (170/100). *Blood:* Plasma protein, 7.1 gm. per cent; A/G ratio, 39/61. N.P.N. 37 mg. per cent. *Course:* Signs and symptoms gradually disappeared. Three months after onset urine and blood pressure normal. *Urine* (26 examinations in 5 months): During 1st month, red cells decreased from 100 ± to 10 ± per h.p.f. and from 10 ± to 2 or 3 ± during 2nd month. In the 3rd, 4th and 5th months no red cells found. Tests for protein negative. *Urinary Proteins*[4] (5 analyses in 12 days, beginning about 2 weeks after onset, when there were 50 ± to 10 ± red cells per h.p.f.):

Date	P.N.	A.N.	T.P.	r.G.%
4– 2–35	0.044	—	0.275	—
4– 5–35	0.031	—	0.194	—
4– 7–35	0.019	—	0.119	—
4– 9–35	0.005	—	0.031	—
4–13–35	0.068	0.023	0.425	66

Case 2. L. G., C. F. of 3½ years. *Diagnosis:* Acute haemorrhagic nephritis. *History:* Onset of oedema about January 27, 1940. Examination showed fever, proteinuria, gross haematuria, oedema, and hypertension (130/95). *Blood:* Plasma protein, 6.1 gm. per cent; A/G ratio 46/54. N.P.N., 35 mg. per cent. *Course:* Signs and symptoms disappeared within 2 months. *Urine* (17 examinations in 3 months): Gross haematuria persisted for 7 or 8 days. During next 3 weeks haematuria decreased to an occasional red cell per h.p.f. Examined 2 and 3 months after onset urine contained no red cells. Tests for protein negative. Blood pressure normal.

Urinary Proteins (4 analyses in 6 days, when gross hematuria was present):

Date	P.N.	A.N.	T.P.	r.G.%
2–2–40	0.032	—	0.200	—
2–4–40	0.030	—	0.188	—
2–5–40	0.020	—	0.125	—
2–7–40	0.004	—	0.025	—

Case 3. H. B., W. M. of 4 years. *Diagnosis:* Acute haemorrhagic nephritis. *History:* Generalized oedema and gross haematuria appeared about November

[4] In this and the following case histories, under the heading *Urinary Proteins* the abbreviations P.N., A.N., and T.P. are used to indicate protein nitrogen, albumin nitrogen, and total protein in grams per cent; and *r.G.%* indicates the relative globulin percentage. The albumin nitrogen and the percentage of globulin could not be accurately determined when the total protein was less than 0.400 grams per cent.

28, 1935, following sore throat and exposure to scarlet fever. *Blood pressure*, 152/95. Serum N.P.N., 66 mg. per cent. *Course:* Gross haematuria occurred irregularly for over a month. The urine gradually returned to normal. All signs and symptoms disappeared. Blood pressure fell to 90/60, and the N.P.N. to 26 mgm. per cent. Four and a half years later, May 26, 1940, urine was normal. *Urine:* Red cells, varying from gross haematuria to occasional cells per h.p.f. found on 19 of 39 examinations in 3 months.

Urinary Proteins (17 analyses in 11 weeks, beginning about a week after onset):

Date	P.N.	A.N.	T.P.	r.G.%
12– 4–35	0.025	—	0.156	—
12– 5–35	0.027	—	0.169	—
12– 6–35	0.013	—	0.081	—
12– 7–35	0.009	—	0.056	—
12–10–35	0.015	—	0.094	—
12–12–35	0.052	—	0.325	—
12–14–35	0.014	—	0.088	—
12–21–35	0.018	—	0.113	—
12–28–35	0.006	—	0.038	—
1– 8–36	0.071	0.035	0.444	51
1– 9–36	0.011	—	0.069	—
1–11–36	0.007	—	0.044	—
1–13–36	0.007	—	0.044	—
1–19–36	0.010	—	0.063	—
1–26–36	0.012	—	0.075	—
2–18–36	0.016	—	0.100	—
2–25–36	0.008	—	0.050	—

Case 4. R. B., W. M. 6 years old. *Diagnosis:* Acute haemorrhagic nephritis. *History:* Oedema and gross haematuria appeared about November 1, 1935, following scarlet fever. Maximum *blood pressure*, 150/100. N.P.N., 94 mg. per cent. *Course:* Signs and symptoms slowly disappeared. Blood pressure and N.P.N. returned to normal. *Urine:* Gross haematuria persisted for about 11 days. Red cells found on 23 of 38 examinations in 9 weeks. None seen on last 5 examinations, about 2½ months from onset. Examined 4½ years later, May 26, 1940, urine was normal.

Urinary Proteins (10 analyses in 2 months, beginning 6 days after onset):

Date	P.N.	A.N.	T.P.	r.G.%
11– 7–35	0.007	—	0.044	—
11–10–35	0.006	—	0.038	—
11–13–35	0.007	—	0.044	—
11–17–35	0.030	—	0.188	—
11–22–35	0.017	—	0.106	—
11–28–35	0.008	—	0.050	—
12– 4–35	0.003	—	0.019	—
12–11–35	0.006	—	0.038	—
12–24–35	0.005	—	0.031	—
1– 1–36	0.015	—	0.094	—

Case 5. R. R., W.M. 13 years old. *Diagnosis:* Acute haemorrhagic nephritis. *History:* Gross haematuria and convulsions appeared September 26, 1935, about 3 weeks after scarlet fever. *Blood pressure*, 150/90. N.P.N., 112 mg. per cent. *Course:* Within 18 days blood pressure was normal and N.P.N. was 49 mg. per cent. Urine contained a trace of protein, occasional red cells. *Urine:* (16 examinations in 20 days): Haematuria varying from gross blood to occasional cells per h.p.f. found 15 times. Examined 4½ years from onset, urine was normal.

Urinary Proteins (6 analyses in 12 days, beginning about 2nd day of disease):

Date	P.N.	A.N.	T.P.	r.G.%
9–27–35	0.058	—	0.363	—
9–29–35	0.014	—	0.088	—
10– 1–35	0.027	—	0.169	—
10– 3–35	0.014	—	0.088	—
10– 6–35	0.014	—	0.088	—
10– 8–35	0.015	—	0.094	—

Case 6. D. G., W.F. 4½ years old. *Diagnosis:* Acute haemorrhagic nephritis *History:* Oedema noticed October 17, 1935, about 3 weeks after scarlet fever. Gross haematuria developed. Anuria for 36 hours. Serum N.P.N., 114 mg. per cent. Maximum *blood pressure*, 106/50. *Urine:* Red cells found on 12 of 32 examinations. Urine contained a trace of protein on discharge from hospital; and also 4½ years later, when serum N.P.N. was 32 mg. per cent, urea clearance 92 and 100 per cent of normal maximum.

Urinary Proteins (6 analyses in 19 days beginning 13 days after onset; 3 analyses 4½ years later):

Date	P.N.	A.N.	T.P.	r.G.%
10–30–35	0.027	—	0.169	—
10–31–35	0.038	—	0.238	—
11– 2–35	0.003	—	0.019	—
11– 4–35	0.006	—	0.038	—
11– 7–35	0.005	—	0.031	—
11–17–35	0.012	—	0.075	—
5–19–40	0.006	—	0.038	—
5–26–40	0.007	—	0.044	—
6– 9–40	0.008	—	0.050	—

Case 7. G. B., W.M. 14 years old. *Diagnosis:* Acute haemorrhagic nephritis. *History:* Onset of headache, oedema and vomiting about 2 weeks after sore throat. Examination showed fever, pharyngitis, sinusitis, septicaemia, (pneumococcus, type 4, two colonies in 6 cc. of blood), gross haematuria, anasarca, plasma protein 5.08 gm. per cent, A/G ratio 54/46, and hypertension (150/108). *Course:* During 3 days in hospital blood N.P.N. fell from 75 to 42 mg. per cent. Pneumonia developed and septicaemia increased to 600 colonies per cc. of blood. Death occurred about a week after onset. *Urine:* 1270 cc. in 80 hours, grossly bloody.

Urinary Proteins (2 analyses in 80 hours, beginning about 3 days from onset):

Date	P.N.	A.N.	T.P.	r.G.%
1–29–35	0.049	—	0.306	—
2– 1–35	0.067	0.042	0.419	37

Kidneys (Autopsy 14065): The lesions are typical of acute diffuse haemorrhagic nephritis. The glomeruli look very cellular. Each tuft of capillaries forms a solid looking wedge-shaped mass in which capillaries seem fused together and appear to contain few red cells. There are polymorphonuclear leucocytes in and between the capillaries. Between capillaries there are also mononuclear cells. Some glomerular epithelial cells are necrotic and some contain "colloid droplets." There is little proliferation of epithelium and there are no crescents. No exudate can be identified in the glomeruli. Sections of the perfused kidney show capillaries to be patent. There is no obstruction by new endothelial cells. Many tubules contain blood, and there are masses of polymorphonuclear leucocytes in some. Occasional tubules contain hyaline material. At the hilum of each glomerulus there is some infiltration by leucocytes.

Case 8. W. C., C.M. 63 years old. *Diagnosis:* Acute haemorrhagic nephritis. *History:* Onset of oedema about the middle of November, 1939, a month before death. "Smoky urine" was observed a week after onset. Examination showed fever, hematuria, anasarca, plasma protein 6.93 gm. per cent, A/G ratio 26/74, blood N.P.N. 90 mg. per cent, urea clearance 19 per cent of normal standard, and hypertension (168/92). *Course:* Oedema and haematuria decreased. *Blood pressure* fell to normal. Fever continued, N.P.N. rose to 144 mg. per cent, and the patient died in uremia. *Urine* (16 examinations in 16 days): Red cells decreased from "too many to count" to 25 or 30 per h.p.f.

Urinary Proteins (11 analyses in 16 days, beginning about 2 weeks after onset):

Date	P.N.	A.N.	T.P.	r.G.%
12– 1–39	0.032	—	0.200	—
12– 2–39	0.027	—	0.169	—
12– 3–39	0.021	—	0.131	—
12– 5–39	0.006	—	0.038	—
12– 6–39	0.007	—	0.044	—
12– 7–39	0.013	—	0.081	—
12– 9–39	0.015	—	0.094	—
12–11–39	0.013	—	0.081	—
12–13–39	0.022	—	0.138	—
12–14–39	0.040	—	0.250	—
12–15–39	0.048	—	0.300	—

Kidneys (Autopsy 16711): The lesions are like those described in Case 7. In addition there is a little proliferation of glomerular visceral epithelium. In occasional glomeruli are a few small masses of clotted fibrin and hyaline material.

In the cortex and in the perirenal tissue are a few necrotic arterioles surrounded by proliferating connective tissue and leucocytes, lesions like periarteritis nodosa. There are a few similar lesions in the gall bladder, about the adrenals and in branches of a popliteal artery.

Case 9. C. E., W.F. of 39 years. *Diagnosis:* Pregnancy and hypertension. *History:* The patient was an obese woman (238 pounds), admitted to the hospital in the 24th week of pregnancy, with generalized oedema, oliguria, dyspnoea and hypertension (198/130). The ankles had been swollen for 2 months. Generalized oedema developed a few days before admission. Oliguria and oedema increased. *Blood pressure* rose to 218/136 and N.P.N. to 40 mg. per cent. *Urine* at first contained many red cells (60 to 75 per h.p.f.), and total protein and globulin in high concentration. *Course:* On the 4th day in the hospital pregnancy was terminated. Proteinuria decreased within a few hours, and almost disappeared within 2 weeks. Blood pressure fell gradually and was 142/106 when last determined, about 4 weeks from admission. When the patient was discharged urea clearance was 83 and 90 per cent of normal maximum.

Urinary Proteins (10 analyses in 15 days):

Date	P.N.	A.N.	T.P.	r.G.%
11– 2–39	0.159	0.103	0.994	35
11– 3–39	0.211	0.131	1.319	38
11– 4–39	0.199	0.096	1.244	52
11– 5–39	0.052	—	0.325	—
11– 6–39	0.063	—	0.394	—
11– 8–39	0.029	—	0.181	—
11–10–39	0.015	—	0.094	—
11–12–39	0.015	—	0.094	—
11–14–39	0.013	—	0.081	—
11–16–39	0.012	—	0.075	—

GROUP 2

Case 1. C. S., W.M. 15 years old. *Diagnosis:* Acute haemorrhagic nephritis. *Duration:* About 2 months. *History:* Oliguria and oedema appeared about April 1, 1935, during recovery from scarlet fever. Examination showed anasarca, gross haematuria, plasma protein 4.69 grams per cent, A/G ratio 41/59, urea clearance 7 per cent of normal standard, and hypertension (170/110). *Course:* Anuria developed, the N.P.N. rose from 130 to 184 mg. per cent, and the patient died in uremia. An autopsy was not performed.

Urinary Proteins (2 analyses in 10 days, beginning about 1½ months after the onset):

Date	P.N.	A.N.	T.P.	r.G.%
5–15–35	0.134	0.066	0.838	51
5–25–35	0.282	0.167	1.763	41

Case 2. C. D., C.M. 27 years old. *Diagnosis:* Acute haemorrhagic nephritis. *History:* About March 10, 1936, onset of headache, dyspnea, oedema and gross haematuria. Examination showed infected pustular lesions on skin, and septicaemia (beta haemolytic streptococcus); fever, anasarca, plasma protein 5.58 grams per cent, A/G ratio 39/61, and hypertension (170/98). *Course:* The N.P.N. rose from 80 to 100. Little urine was excreted, and the patient died in coma on the 3rd day in hospital, about 1 or 2 weeks from onset.

Urinary Proteins (2 analyses in 3 days):

Date	P.N.	A.N.	T.P.	r.G.%
3–15–36	0.218	0.129	1.363	41
3–16–36	0.172	0.095	1.075	45

Kidneys (Autopsy 14698): The glomerular lesions are very similar to those in cases 7 and 8 of group 1. The glomeruli have the same solid, cellular appearance, due to leucocytes in the capillaries and between them. There are new epithelial cells between some capillaries. In the perfused kidney capillaries are patent. There is no proliferation of endothelium.

In addition to these changes, most glomeruli contain clots of fibrinous exudate and red cells in Bowman's space and between tufts of capillaries. Some of these are partially covered by epithelium. Practically no fibrin or hyaline exudate can be found between or surrounding individual capillary loops. Many tubules contain blood. Some are partly filled with leucocytes. In a few are casts of fibrin.

GROUP 3

Case 1. M. P., C.F. 15 months old. *Diagnosis:* Lipoid nephrosis. *History:* Oedema, noticed in July, 1935, progressed to anasarca. Signs and symptoms disappeared within 7 months. Urine was normal 7 months, 11 months and 5 years after onset. Plasma proteins rose from 4.2 to 6.4 grams per cent. Blood cholesterol fell from 1200 to 157 mg. per cent. Maximum *blood pressure*, 116/78. Blood N.P.N. (26 determinations) usually below 35 mg. per cent. *Urine* (22 examinations): Occasional red cells per h.p.f. found 3 times. Cholesterol esters present.

Urinary Proteins (17 analyses in 4 months, beginning 2½ months after the onset):

Date	P.N.	A.N.	T.P.	r.G.%
9–19–35	0.110	0.084	0.688	24
9–20–35	0.114	0.121	0.900	16
10– 5–35	0.059	—	0.369	—
10–17–35	0.080	0.070	0.500	12
10–23–35	0.221	0.169	1.380	24
10–30–35	0.056	—	0.350	—
11– 7–35	0.062	—	0.388	—
11–16–35	0.036	—	0.225	—

Date	P.N.	A.N.	T.P.	r.G.%
11–24–35	0.033	—	0.206	—
12– 1–35	0.049	—	0.306	—
12– 8–35	0.028	—	0.175	—
12–16–35	0.005	—	0.031	—
12–23–35	0.014	—	0.088	—
12–31–35	0.010	—	0.063	—
1–11–36	0.034	—	0.213	—
1–13–36	0.043	—	0.269	—
1–27–36	0.014	—	0.088	—

Case 2. B. L., W.M. 3 years old. *Diagnosis:* Lipoid nephrosis. *History:* Onset with oedema September, 1935. Anasarca developed. Plasma proteins rose from 4.3 (A/G ratio between 43/57 and 37/63) to 5.9 gm. per cent in 2 months. Oedema disappeared in about 3.5 months. Maximum *blood pressure*, 110/70. Highest blood cholesterol, 1500 mg. per cent, and N.P.N., 44 mg. per cent. *Course:* Urine, blood cholesterol, and phthalein excretion normal a year after onset. *Urine* (27 examinations in 7 months): Cholesterol esters were present, and 3 to 5 red cells per h.p.f. were found six times. Examined at intervals for 4 years after recovery, urine has always been normal.

Urinary Proteins (16 analyses in 5 months beginning 1 month after the onset):

Date	P.N.	A.N.	T.P.	r.G.%
10– 5–35	0.092	0.088	0.575	4
10– 8–35	0.080	0.064	0.500	20
10–15–35	0.127	0.120	0.794	6
10–22–35	0.053	—	0.331	—
10–30–35	0.073	0.044	0.456	40
11– 6–35	0.004	—	0.025	—
11–16–35	0.032	—	0.200	—
11–23–35	0.005	—	0.031	—
11–30–35	0.025	—	0.156	—
12–10–35	0.003	—	0.019	—
12–17–35	0.019	—	0.119	—
12–31–35	0.041	—	0.256	—
1–12–36	0.169	0.062	1.056	63
1–24–36	0.037	—	0.231	—
1–28–36	0.008	—	0.050	—
3–17–36	0.004	—	0.025	—

Case 3. V. H., W.F. 15 years old. *Diagnosis:* Lipoid nephrosis. *History:* Onset in October, 1935, with anasarca. Plasma proteins between 2.5 and 3.5 grams per cent; A/G ratio from 38/62 to 23/77. Blood cholesterol 650, N.P.N. 25 to 30 mg. per cent. Urea clearance 62 and 68 per cent of normal maximum. *Blood pressure* normal (110–112/70). *Course:* About 7 months after onset, there were several periods, lasting a few days, characterized by fever, abdominal pain, vomiting and diarrhoea, probably due to peritonitis. During and after these

periods diuresis and loss of oedema occurred, and thereafter the urine returned to normal. In 1940, nearly 5 years after onset, blood pressure was 112/70, N.P.N. 24 mg. per cent, urea clearance 100 and 115 per cent of normal maximum, and urine normal. *Urine* (9 examinations during a month in hospital, 3 months after onset): Occasional red cells per h.p.f. found 8 times. Crystals of cholesterol esters present.

Urinary Proteins (7 analyses in 1 month, 3 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
1–29–36	0.192	0.163	1.200	15
2– 1–36	0.218	0.170	1.363	22
2– 5–36	0.295	0.216	1.844	27
2– 8–36	0.172	0.166	1.075	3
2–15–36	0.099	0.092	0.619	7
2–22–36	0.158	0.126	0.988	20
2–29–36	0.213	0.135	1.331	37
6–26–40	0.000	—	0.000	—
7– 2–40	0.000	—	0.000	—

Case 4. L. K., W.F. 2 years old. *Diagnosis:* Lipoid nephrosis. *History:* Oedema observed in July, 1935, became generalized. *Blood pressure* usually normal, 130/75 once. Blood cholesterol 769 and maximum urea nitrogen, 32 mg. per cent. *Course:* Oedema decreased and was slight after 4 months of disease. Proteinuria disappeared within 1.5 years. The urine, in 1937, 1938, 1939 and 1940 was always normal. *Urine:* Contained doubly-refractile cholesterol esters; and from 1 to 15 red cells per h.p.f. on 31 of 37 examinations.

Urinary Proteins (39 analyses in 13 months beginning 3 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
10– 9–35	0.092	0.090	0.575	2
10–16–35	0.219	0.201	1.369	9
10–21–35	0.184	0.156	0.150	15
10–28–35	0.061	—	0.381	—
11– 6–35	0.232	0.172	1.450	26
11–13–35	0.096	0.095	0.600	1
11–20–35	0.096	0.086	0.600	10
11–27–35	0.165	0.151	1.031	8
12– 4–35	0.174	0.163	1.088	6
12–11–35	0.051	—	0.319	—
12–18–35	0.078	0.073	0.488	6
12–25–35	0.022	—	0.138	—
1– 1–36	0.194	0.145	1.213	25
1– 8–36	0.130	0.077	0.813	41
1–15–36	0.052	—	0.325	—
1–23–36	0.098	0.083	0.613	15
1–29–36	0.055	—	0.344	—
2– 5–36	0.030	—	0.187	—

Date	P.N.	A.N.	T.P.	r.G.%
2–12–36	0.043	—	0.269	—
2–19–36	0.063	—	0.394	—
3– 4–36	0.083	0.043	0.519	48
3–11–36	0.040	—	0.250	—
3–18–36	0.045	—	0.281	—
3–25–36	0.088	0.082	0.550	7
4– 1–36	0.064	0.055	0.400	14
4– 8–36	0.064	0.050	0.400	22
4–15–36	0.040	—	0.288	—
4–22–36	0.020	—	0.125	—
4–28–36	0.059	—	0.369	—
5– 5–36	0.069	0.059	0.431	14
5–12–36	0.055	—	0.344	—
5–19–36	0.083	0.066	0.519	20
5–26–36	0.110	0.096	0.688	13
6– 2–36	0.061	—	0.381	—
9– 1–36	0.008	—	0.050	—
9–16–36	0.023	—	0.144	—
9–30–36	0.015	—	0.094	—
10–14–36	0.020	—	0.125	—
10–28–36	0.054	—	0.338	—
11–30–36	—	—	trace	—
1937, 1938, 1939, 1940			0	—

Case 5. S. D., W.M. 7 years old. *Diagnosis:* Lipoid nephrosis. *History:* In June, 1935, oedema developed, became generalized. For 4 years proteinuria, hypoprōteinaemia and oedema varied. *Blood pressure* usually normal; elevated at times with oliguria (maximum, 134/90). Blood N.P.N. usually normal; 41 mg. per cent once. Maximum blood cholesterol, 984 mg. per cent. Plasma A/G ratio as low as 34/66. *Course:* The patient developed pneumococcal septicaemia and peritonitis twice. During the summer of 1939, proteinuria disappeared. The urine, examined at nearly weekly intervals for over a year thereafter was always normal. In May, 1940, urea clearance was 68 and 72 per cent of normal maximum; blood N.P.N., 30 mg. per cent. *Urine* (169 examinations in 4 years): Red cells varying from rare to 20 per h.p.f. found on 51 examinations. Cholesterol esters usually present.

Urinary Proteins (45 analyses, 35 during 9 months in 1935–36, beginning 2 months after onset, and 10 analyses during 3.5 months in 1939):

Date	P.N.	A.N.	T.P.	r.G.%
9– 5–35	0.094	0.082	0.588	13
9–10–35	0.092	0.060	0.575	35
9–17–35	0.206	0.160	1.288	22
9–23–35	0.163	0.107	1.019	34
10– 3–35	0.131	0.096	0.819	27
10– 8–35	0.284	0.242	1.775	15

Date	P.N.	A.N.	T.P.	r.G.%
10–16–35	0.117	0.086	0.731	26
10–21–35	0.122	0.097	0.763	20
10–28–35	0.332	0.314	2.075	5
11– 5–35	0.058	—	0.363	—
11–11–35	0.216	0.153	1.350	29
11–18–35	0.106	0.092	0.663	13
11–27–35	0.017	—	0.106	—
12– 4–35	0.047	—	0.294	—
12–11–35	0.041	—	0.256	—
12–18–35	0.026	—	0.163	—
12–25–35	0.062	—	0.388	—
1– 1–36	0.055	—	0.344	—
1– 8–36	0.121	0.096	0.756	21
1–15–36	0.050	—	0.313	—
1–23–36	0.083	0.056	0.519	33
1–29–36	0.094	0.080	0.588	15
2– 5–36	0.146	0.119	0.913	18
2–12–36	0.299	0.212	1.869	29
2–19–36	0.095	0.091	0.594	4
3– 4–36	0.035	—	0.219	—
3–11–36	0.079	0.041	0.494	48
3–19–36	0.012	—	0.075	—
3–25–36	0.006	—	0.038	—
4– 1–36	0.004	—	0.025	—
4– 8–36	0.010	—	0.063	—
4–15–36	0.005	—	0.031	—
5– 5–36	0.003	—	0.019	—
5–12–36	0.007	—	0.044	—
5–19–36	0.000	—	0.000	—
5–26–36	0.010	—	0.063	—
2–25–39	0.154	0.138	0.963	10
3– 4–39	0.153	0.102	0.956	33
3–10–39	0.226	0.193	1.413	15
3–18–39	0.106	0.097	0.663	8
3–24–39	0.090	0.074	0.563	18
3–30–39	0.084	0.079	0.525	6
4– 7–39	0.056	—	0.350	—
4–20–39	0.006	—	0.038	—
4–27–39	0.007	—	0.044	—
5– 4–39	0.012	—	0.075	—
9–23–39	0.000	—	0.000	—
9–30–39 to 9–29–40 (36 examinations): negative (Esbach)				

Case 6. W. L., C.M. 20 years old. *Diagnosis:* Lipoid nephrosis. *History:* Oedema in June, 1937, progressed to anasarca. *Blood pressure* always normal; N.P.N. usually around 30 mg. per cent. Urea clearance (4 tests in 15 months) varied from 84 to 240 per cent of normal standard. *Course:* Within about a year

from onset, plasma proteins rose from 2.22 to 6.14 gm. per cent; A/G ratio from 21/79 to 48/52. Blood cholesterol fell from 882 to 285 mg. per cent. Oedema decreased and by the end of January, 1940, urine contained only 0.056 grams per cent of protein. Blood pressure and urea clearance normal (142 to 165 per cent of normal standard). In November, 1940, there was 0.019 grams per cent of protein in the urine. *Urine* (117 examinations): Cholesterol esters present, and red cells, from 1 to 20 per h.p.f. found 80 times.

Urinary proteins (24 analyses in 10 months, beginning 1 year and 5 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
3–24–39	0.154	0.120	0.963	22
3–30–39	0.144	0.075	0.900	48
4– 7–39	0.097	0.067	0.606	31
4–15–39	0.091	0.076	0.569	16
4–20–39	0.097	0.077	0.606	21
4–27–39	0.086	0.068	0.538	21
5– 9–39	0.094	0.081	0.588	14
5–12–39	0.087	0.071	0.544	18
5–18–39	0.089	0.074	0.556	17
5–25–39	0.062	—	0.388	—
6– 1–39	0.078	0.063	0.488	19
6– 8–39	0.061	—	0.381	—
9–23–39	0.046	—	0.288	—
9–30–39	0.053	—	0.331	—
10– 7–39	0.027	—	0.169	—
10–14–39	0.036	—	0.225	—
10–28–39	0.042	—	0.263	—
11– 4–39	0.031	—	0.194	—
11–11–39	0.034	—	0.213	—
11–18–39	0.023	—	0.144	—
11–25–39	0.030	—	0.188	—
12– 9–39	0.014	—	0.088	—
12–16–39	0.021	—	0.131	—
1–20–40	0.009	—	0.056	—
1–27–40	—	—	trace	—

Case 7. M. K., W.F. 20 years old. *Diagnosis:* Nephrotic nephritis. *History:* Onset in January, 1935, with oliguria and oedema. Gross haematuria for several days about 3 months after onset. Plasma proteins usually above 4 grams per cent; A/G ratio often between 33/67 and 19/81. Blood cholesterol, 600 mg. per cent, maximum; N.P.N. usually below 30, reached 38 mg. per cent once. *Blood pressure* nearly always normal, 138/90 once. *Course:* Oedema almost disappeared in 5 months. Urea clearance (15 determinations in 8 months), usually about 80 per cent of normal standard, 98 to 100 per cent of normal standard on discharge from hospital, about 10 months from onset. Proteinuria, never high, decreased

to a trace, 4.5 and 5.5 years after onset. Blood pressure taken at intervals for 2.5 years was normal. In 1939 and in 1940, about 6 years from onset, urine contained only a trace of protein. *Urine* (105 examinations in 3 months), showed doubly refractile cholesterol crystals; and red cells varying from 2 ± to 75 ± per h.p.f. always found.

Urinary Proteins (12 analyses in 9 months, beginning 2 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
3– 7–35	0.156	0.124	0.975	21
4– 4–35	0.102	0.090	0.638	12
4–19–35	0.099	0.048	0.619	53
5–11–35	0.034	—	0.213	—
5–23–35	0.044	—	0.275	—
6– 1–35	0.103	0.058	0.644	44
10–12–35	0.034	—	0.213	—
10–16–35	0.057	—	0.356	—
11–28–35	0.020	—	0.125	—
12– 5–35	0.037	—	0.231	—
12–12–35	0.084	0.072	0.525	14
12–19–35	0.021	—	0.131	—
11– 3–39	—	—	trace	—
6–16–40	—	—	trace	—

Case 8. R. D., W.M. 17 years old. *Diagnosis:* Nephrotic nephritis. *History:* Onset of oedema in July, 1935. Gross haematuria and anuria 3 weeks later. During 10 months in hospital signs and symptoms varied. Plasma protein usually between 3.06 and 3.69 gm. per cent; A/G ratio from 50/50 to 24/76. Blood N.P.N., determined 39 times, usually below 30, reached 46 mg. per cent once. Blood pressure often elevated, 164/100 maximum. *Course:* Urine usually contained more than 1 per cent of protein; a high proportion of globulin on only 4 of 46 analyses. The 1st urea clearance, during increasing anasarca, 53 and 57 per cent of normal standard. Subsequent tests, 4 between November, 1935, and September, 1936, varied between 85 and 150 per cent of normal standard. Four years after onset, blood pressure 120/90, urea clearance 75 and 76 per cent of normal standard and slight proteinuria (0.031 and 0.044 gm. per cent). *Urine:* From 1 ± to 10 ± red cells per h.p.f. seen on 185 of 215 examinations in 10 months. Cholesterol esters present.

Urinary Proteins (46 analyses in 13 months, beginning 2 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
9–14–35	0.045	—	0.281	—
9–21–35	0.156	0.152	0.975	3
9–29–35	0.116	0.094	0.725	19
10– 9–35	0.333	0.262	2.081	21
10–19–35	0.309	0.217	1.931	30
10–26–35	0.294	0.178	1.838	39
11– 2–35	0.223	0.217	1.394	3

Date	P.N.	A.N.	T.P.	r.G.%
11- 9-35	0.296	0.271	1.850	9
11-16-35	0.286	0.269	1.788	6
11-23-35	0.214	0.178	1.338	17
11-30-35	0.254	0.208	1.588	19
12- 7-35	0.202	0.138	1.263	32
12-14-35	0.264	0.224	1.650	15
12-21-35	0.181	0.146	1.131	19
12-28-35	0.396	0.282	2.475	29
1- 4-36	0.197	0.159	1.231	19
1-11-36	0.285	0.240	1.781	16
1-18-36	0.391	0.365	2.444	7
1-26-36	0.270	0.179	1.688	34
2- 1-36	0.482	0.400	3.013	17
2- 8-36	0.403	0.303	2.519	25
2-15-36	0.453	0.372	2.831	18
2-22-36	0.238	0.200	1.488	16
2-29-36	0.506	0.369	3.163	27
3- 4-36	0.364	0.294	2.275	19
3-14-36	0.269	0.240	1.681	11
3-22-36	0.249	0.163	1.556	35
3-29-36	0.266	0.210	1.663	21
4- 5-36	0.182	0.162	1.138	11
4-12-36	0.272	0.253	1.700	7
4-19-36	0.197	0.177	1.231	10
4-26-36	0.244	0.229	1.525	6
5- 4-36	0.185	0.159	1.156	14
5-11-36	0.204	0.157	1.275	23
6-13-36	0.211	0.191	1.319	9
6-21-36	0.227	0.200	1.419	12
6-27-36	0.261	0.213	1.631	18
7- 9-36	0.240	0.193	1.500	19
7-20-36	0.164	0.122	1.025	26
8- 4-36	0.143	0.133	0.894	7
8-11-36	0.038	—	0.238	—
8-17-36	0.169	0.159	1.056	6
9- 1-36	0.134	0.131	0.838	2
9-20-36	0.081	0.079	0.506	2
10- 3-36	0.097	0.094	0.606	3
10-25-36	0.098	0.095	0.613	3
6-19-40	0.005	—	0.031	—
7- 1-40	0.007	—	0.044	—

Case 9. I. S., C.F. 40 years old. *Diagnosis:* Nephrotic nephritis. *Outcome:* The disease persists, with slight change in renal function during 2 years, usually slight to moderate proteinuria, and high globulinuria occasionally. *History:* Headache and oedema in April, 1939. During the following 2 years, signs and symptoms varied. Never more than moderate oedema. Plasma proteins some-

what decreased (5.09 gm. per cent; A/G ratio 44/56). Maximum blood cholesterol (2 determinations), 441 mg. per cent. *Blood pressure* often moderately elevated, maximum 160/120. *Renal Function:* Urea clearance in May, 1939, 56 and 57 per cent of normal standard. Eight months later it was 43 and 41 per cent of normal standard; in June, 1940, 49 and 47 per cent of normal standard, and in March, 1941, about 2 years from onset, 38 and 40 per cent of normal standard. *Urine:* Red cells varying from 1 ± to 8 ± per h.p.f. on 23 of 41 examinations. Crystals of cholesterol esters present

Urinary Proteins (82 analyses in 22 months, beginning about 3 weeks after onset):

Date	P.N.	A.N.	T.P.	r.G.%
5-22-39	0.025	—	0.156	—
5-27-39	0.044	—	0.275	—
6- 1-39	0.031	—	0.194	—
6- 8-39	0.041	—	0.256	—
6-15-39	0.034	—	0.213	—
9-30-39	0.117	0.080	0.731	32
10- 7-39	0.161	0.120	1.006	25
10-14-39	0.086	0.061	0.538	29
10-21-39	0.166	0.119	1.038	29
10-28-39	0.154	0.110	0.963	29
11- 4-39	0.126	0.094	0.788	25
11-11-39	0.161	0.116	1.006	28
11-18-39	0.164	0.116	1.025	29
11-25-39	0.164	0.118	1.025	28
12- 2-39	0.143	0.101	0.894	29
12- 9-39	0.098	0.074	0.613	24
12-16-39	0.139	0.105	0.869	25
12-24-39	0.109	0.080	0.681	27
12-30-39	0.298	0.273	1.863	8
1- 6-40	0.084	0.063	0.525	25
1-13-40	0.080	0.062	0.500	22
1-20-40	0.073	0.059	0.456	19
1-27-40	0.072	0.059	0.450	18
2- 3-40	0.054	—	0.338	—
2-10-40	0.060	—	0.375	—
2-17-40	0.063	—	0.394	—
2-24-40	0.058	—	0.363	—
3- 3-40	0.058	—	0.363	—
3- 9-40	0.030	—	0.188	—
3-16-40	0.097	0.080	0.606	18
3-23-40	0.065	0.050	0.406	23
3-30-40	0.048	—	0.300	—
4- 6-40	0.057	—	0.356	—
4-13-40	0.093	0.074	0.581	21
4-20-40	0.096	0.073	0.600	24
4-27-40	0.019	—	0.119	—

Date	P.N.	A.N.	T.P.	r.G.%
5- 4-40	0.048	—	0.300	—
5-11-40	0.070	0.058	0.438	17
5-18-40	0.067	0.052	0.419	22
5-26-40	0.049	—	0.306	—
6- 2-40	0.050	—	0.313	—
6-10-40	0.036	—	0.225	—
6-16-40	0.046	—	0.288	—
6-23-40	0.093	0.076	0.581	18
6-30-40	0.064	0.054	0.400	16
7- 7-40	0.084	0.067	0.525	20
7-14-40	0.067	0.061	0.419	9
7-21-40	0.033	—	0.206	—
7-28-40	0.043	—	0.269	—
8- 4-40	0.089	0.062	0.556	30
8-11-40	0.085	0.070	0.531	18
8-18-40	0.039	—	0.244	—
8-25-40	0.075	0.069	0.469	9
9- 1-40	0.101	0.084	0.631	17
9- 8-40	0.065	0.058	0.406	11
9-16-40	0.066	0.055	0.413	17
9-22-40	0.036	—	0.225	—
9-29-40	0.099	0.091	0.619	8
10- 6-40	0.074	0.066	0.463	11
10-13-40	0.069	0.062	0.431	10
10-20-40	0.071	0.058	0.444	18
10-26-40	0.098	0.076	0.613	23
11- 2-40	0.095	0.074	0.594	21
11- 9-40	0.102	0.081	0.638	21
11-16-40	0.079	0.055	0.594	30
11-21-40	0.108	0.086	0.675	20
11-30-40	0.073	0.057	0.456	22
12- 7-40	0.120	0.086	0.750	28
12-14-40	0.085	0.067	0.531	21
12-21-40	0.062	0.051	0.388	18
12-28-40	0.079	0.059	0.494	25
1- 4-41	0.089	0.069	0.556	22
1-11-41	0.108	0.084	0.685	22
1-18-41	0.150	0.100	0.938	33
1-25-41	0.053	0.052	0.331	2
2- 1-41	0.041	0.027	0.256	34
2- 8-41	0.052	0.039	0.325	25
2-15-41	0.110	0.085	0.688	23
2-22-41	0.100	0.074	0.625	26
3- 1-41	0.154	0.114	0.963	26
3- 8-41	0.115	0.083	0.719	28
3-15-41	0.123	0.084	0.769	32
3-22-41	0.163	0.119	1.015	27
3-29-41	0.132	0.102	0.825	23

Case 10. H. M., W.F. 13 years old. *Diagnosis:* Nephrotic nephritis. *Outcome:* Disease persists, with hypertension, at end of 2¼ years. Renal function nearly stationary. Moderate proteinuria usually and high globulinuria uncommonly. *History:* Oedema noticed in November, 1938, and gross haematuria the following April. During a month in hospital plasma proteins were usually about 4 gm. per cent; A/G ratio varied from 76/24 to 55/45. Serum cholesterol as high as 387 mg. per cent. *Course:* Observed since April, 1939, oedema has varied from slight to moderate. *Blood pressure* has been moderately elevated often, 160/104 the highest. *Renal Function:* The 1st urea clearance, in April, 1939, was 35 and 35 per cent of normal standard. During the following 2 years it has been variable, but has perhaps decreased slightly. In May, 1939, the clearance was 43 and 44 per cent of normal standard, in June 50 per cent of normal standard and 36 per cent of normal maximum; in March, 1941, 40 and 41 per cent of normal maximum. *Urine* (67 examinations): Crystals of cholesterol esters present, and red cells, varying from 1 ± to 90 ± per h.p.f. always found.

Urinary Proteins (84 analyses in 22 months, beginning about 6 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
5–12–39	0.072	0.063	0.450	12
5–18–39	0.057	—	0.356	—
5–26–39	0.052	—	0.325	—
6– 1–39	0.049	—	0.306	—
6– 8–39	0.038	—	0.238	—
9–30–39	0.070	0.064	0.438	9
10– 7–39	0.054	—	0.338	—
10–14–39	0.062	—	0.388	—
10–21–39	0.056	—	0.350	—
10–28–39	0.073	0.065	0.456	11
11– 4–39	0.048	—	0.300	—
11–11–39	0.062	—	0.388	—
11–18–39	0.039	—	0.244	—
11–26–39	0.077	0.067	0.481	13
12– 2–39	0.075	0.067	0.469	11
12– 9–39	0.079	0.074	0.494	6
12–18–39	0.062	—	0.388	—
12–21–39	0.069	0.063	0.431	9
12–30–39	0.087	0.082	0.544	6
1– 6–40	0.124	0.112	0.775	10
1–13–40	0.085	0.070	0.531	18
1–20–40	0.111	0.095	0.694	14
1–27–40	0.090	0.072	0.563	20
2– 3–40	0.086	0.071	0.538	17
2–10–40	0.110	0.087	0.688	21
2–17–40	0.102	0.088	0.638	14
2–24–40	0.098	0.082	0.613	16
3– 2–40	0.128	0.098	0.800	23

Date	P.N.	A.N.	T.P.	r.G.%
3- 9-40	0.075	—	0.469	—
3-16-40	0.100	0.081	0.625	19
3-23-40	0.126	0.099	0.788	22
3-30-40	0.100	0.080	0.625	20
4- 6-40	0.118	0.100	0.738	15
4-13-40	0.093	0.075	0.581	19
4-20-40	0.095	0.077	0.594	19
4-27-40	0.119	0.097	0.744	18
5- 4-40	0.093	0.074	0.581	19
5-11-40	0.088	0.071	0.550	20
5-18-40	0.114	0.080	0.713	30
5-26-40	0.103	0.079	0.644	23
6- 2-40	0.102	0.081	0.638	21
6-12-40	0.089	0.067	0.556	24
6-16-40	0.110	0.087	0.688	21
6-23-40	0.105	0.084	0.656	20
6-30-40	0.101	0.085	0.631	16
7- 7-40	0.095	0.075	0.594	21
7-14-40	0.132	0.105	0.825	22
7-21-40	0.093	0.076	0.581	18
7-28-40	0.071	0.053	0.444	25
8- 4-40	0.098	0.078	0.613	20
8-11-40	0.060	—	0.375	—
8-18-40	0.085	0.073	0.531	14
8-25-40	0.095	0.079	0.594	17
9- 1-40	0.065	0.053	0.406	18
9- 8-40	0.078	0.067	0.488	14
9-16-40	0.090	0.073	0.563	19
9-22-40	0.077	0.063	0.481	18
9-29-40	0.089	0.072	0.556	19
10- 6-40	0.086	0.071	0.538	17
10-13-40	0.068	0.054	0.425	22
10-20-40	0.078	0.063	0.488	19
10-26-40	0.098	0.085	0.613	13
11- 2-40	0.095	0.070	0.594	26
11- 9-40	0.108	0.076	0.675	30
11-16-40	0.113	0.076	0.706	33
11-24-40	0.090	0.062	0.563	31
11-30-40	0.105	0.083	0.656	21
12- 7-40	0.096	0.076	0.600	21
12-14-40	0.118	0.092	0.738	22
12-21-40	0.129	0.104	0.806	19
12-28-40	0.181	0.130	1.131	28
1- 4-41	0.156	0.115	0.975	26
1-11-41	0.134	0.104	0.838	22
1-18-41	0.101	0.081	0.631	20
1-25-41	0.110	0.082	0.688	25

Date	P.N.	A.N.	T.P.	r.G.%
2- 1-41	0.122	0.092	0.763	25
2- 8-41	0.094	0.073	0.588	22
2-15-41	0.110	0.085	0.688	23
2-22-41	0.103	0.077	0.644	25
3- 1-41	0.076	0.059	0.475	22
3- 8-41	0.090	0.070	0.563	23
3-15-41	0.098	0.072	0.613	27
3-23-41	0.099	0.079	0.619	20
3-29-41	0.095	0.073	0.594	23

GROUP 4

Case 1. M. H., C.F. 20 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Oedema of legs in March, 1934. The patient was examined in July and died the following September. There was moderate oedema. Plasma proteins, 5.95 gm. per cent., A/G ratio 39/61. Blood N.P.N. was 68, and rose to 224 mg. per cent. Maximum *blood pressure*, 250/150. *Urine:* Red cells, from 1 to 4 per h.p.f. found on 20 of 27 examinations.

Urinary Proteins (1 analysis):

Date	P.N.	A.N.	T.P.	r.G.%
9-15-34	0.191	0.109	1.193	43

Kidneys (Autopsy 13851): Most tubules are atrophied and lie in scarred interstitial tissue in which there are foci of lymphocytes. At wide intervals are patches of dilated tubules in normal interstitial tissue. Many are distended by a homogeneous, hyaline, eosinophilic material. There are fresh clots of fibrin, without red cells, in occasional tubules, and a few contain leucocytes.

None of the glomeruli is normal. Some are small and completely hyalinized. Some lie compressed in parts of Bowman's capsules which are chiefly occupied by large, hyalinized crescents. In some glomeruli there is a fairly cellular and in others less cellular hyaline material. It lies between tufts of capillaries, and between and around individual capillary loops. The walls of some capillaries are infiltrated and thickened by hyaline material. There is moderate proliferation of glomerular epithelium. The cells form single layers over segments of glomeruli, and there are some small, thin, epithelial crescents. Some of the cells are swollen and contain "colloid droplets." Some of the intrarenal arteries show slight thickening of the intima. With search a few necrotic arterioles are found.

Case 2. G. B., W.M., 18 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* The 1st symptom was oedema in September, 1934. The patient was examined in April and died in May, 1935. There was anasarca, hypertension (blood pressure usually about 150/100), plasma proteins 4.73 gm. per cent; A/G ratio 41/59. Blood N.P.N. rose in about a month from 164 to 240 mg. per cent. *Urine* (29 examinations): Red cells always found, and varied from 5 ± to 60 ± per h.p.f.

Urinary Proteins (1 analysis, 8 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
5–2–35	0.557	0.323	3.481	42

Kidneys (Autopsy 14194): Glomeruli of two varieties are found. Deep in the cortex are moderate numbers of small glomeruli, almost completely replaced by rather acellular, stratified, hyaline, scar-like tissue. The majority of glomeruli show alterations which are similar in all, but vary in degree. These are greatly enlarged, measuring from 250 to 350 μ in diameter. Some are more than twice as large as normal. The tufts of capillaries form large fan-shaped masses of dense, eosinophilic material which surrounds the individual capillary loops, lies between them, and has infiltrated and thickened the walls of some. In some areas there are few and in others many mononuclear connective tissue cells. Some capillaries contain numerous polymorphonuclear leucocytes. Sections of one kidney perfused at autopsy show patent capillaries and endothelial cells in normal numbers.

Most tubules are atrophied and there is moderate scarring of the interstitial tissue which is infiltrated in places with lymphocytes. There are scattered groups of tubules which are relatively normal, but many of these are distended by dense hyaline material which stains like that around the glomerular capillaries, and has caused pressure atrophy of the tubular epithelium. Fresh blood is found in few tubules. The intra-renal arteries show slight thickening of the intima. In the walls of some of the glomerular arterioles small hyaline areas can be found.

Case 3. J. B., C.M. 51 years old. *Diagnosis:* Subacute nephrotic nephritis. *History:* Oedema appeared in February, 1934, and was variable until death, April 20, 1936. Examinations in March and April, 1936, showed anasarca, low plasma protein (4.5 and 4.63 gm. per cent), inverted A/G ratio (31/69 and 14/86), normal *blood pressure* at times, and hypertension at times (maximum, 168/104). *Renal Function:* Between March 14 and April 11 urea clearance fell from 70 and 82 to 25 and 22 per cent of normal standard. Blood N.P.N. rose from 29 to 75 gm. per cent. *Urine* (34 examinations): Red cells always found, varying from about 1 to 15 per h.p.f.

Urinary Proteins (2 determinations in 13 days, beginning about a year after onset):

Date	P.N.	A.N.	T.P.	r.G.%
3–31–36	0.105	0.052	0.656	50
4–12–36	0.044	—	0.275	—

Kidneys (Autopsy 14173): The glomeruli are all nearly exactly alike. The walls of glomerular capillaries are slightly to moderately infiltrated and surrounded by a smooth, homogeneous, hyaline material which in places has collected between capillaries to form irregular masses varying in size up to 20 μ in diameter. The walls of individual capillary loops infiltrated by the hyaline material measure from

2 to 4 μ in thickness. There is slight proliferation of visceral epithelium and there are occasional small epithelial crescents. Fresh blood can be found in few tubules. There are few small scattered foci of moderately atrophied tubules in slightly scarred interstitial tissue. The intrarenal arteries and arterioles show no sclerosis. Sections of the perfused kidney show patent capillaries and no proliferation of endothelium.

Case 4. M. C., C.F. 29 years old. *Diagnosis:* Subacute nephrotic nephritis. *History:* The disease began with oedema and joint pains in November, 1935. The patient died in uremia nine weeks later. She was studied during the last 5½ weeks of the disease. *Blood pressure* was normal (114/64). The plasma protein was 5.16 gm. per cent, A/G ratio 34/66, blood N.P.N. 26, and serum cholesterol 174 mg. per cent. Urea clearance was 29 and 32 per cent of normal standard. *Course:* Within a month oedema increased, plasma protein fell to 3.85 gm. per cent, A/G ratio to 19/81, and N.P.N. rose to 108. The urea clearance fell to 0.52 and 1.23 per cent of normal standard. Blood pressure was never elevated. *Urine* (27 examinations): Red cells varying from about 1 to 20 per h.p.f. found 21 times.

Urinary Porteins (4 analyses in last 2 weeks of the disease):

Date	P.N.	A.N.	T.P.	r.G.%
12–23–35	0.261	0.094	1.631	64
12–28–35	0.104	0.044	0.650	58
1– 6–36	0.101	0.040	0.631	60
1– 8–36	0.323	0.120	2.019	63

Kidneys (Autopsy 14598): All glomeruli contain capillaries which look slightly thicker than normal. Under the oil immersion lens many capillary loops are slightly infiltrated by a hyaline material which also collects around some of them in layers of varying thickness. The wall of the thickest loop found measures 4 μ. There are also a few isolated irregular globules of dense hyaline material between loops of capillaries, the largest measuring 6.5 μ in diameter. There is very slight increase in the number of cells between capillaries, but no evidence of proliferating endothelium or excessive leucocytes in capillaries. There are a few small epithelial crescents, and a few new large basophilic epithelial cells are found over the tips of occasional capillary loops.

Most tubules in the cortex are separated by a small amount of new interstitial scar tissue. Most tubules are wider than normal. The epithelium of many shows cloudy swelling. Many tubules are greatly dilated and are obstructed by hyaline material and there is marked pressure atrophy of the epithelium. The material in a few tubules consists of fresh and compact fibrin. Most of the hyaline material is smoothly homogeneous. In some it forms irregular masses with sharp angles, and in some rounded globular masses. There is fresh blood in occasional tubules. The intrarenal arteries show no thickening of the intima or hyaline arteriolosclerosis.

Case 5. T. B., C.F. 25 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Onset of oedema in February, 1934. The disease was characterized by steady loss of renal function, variable oedema, and increasing hypertension over a period of about 3 years. In 1934 plasma protein was 4.68 gm. per cent, A/G ratio 22/78, and urea clearance decreased from 80 to 59 per cent of normal standard. In 1935 plasma protein, still low, consisted usually of about 65 per cent globulin. Urea clearance varied between 24.5 and 42 per cent of normal standard (2 tests). In 1936 the patient died in coma. *Urine:* Red cells, varying from about 1 to 21 per h.p.f., found on 72 of 76 examinations.

Urinary Proteins (5 analyses in 2½ weeks in 1935, nearly 2 years after onset):

Date	P.N.	A.N.	T.P.	r.G.%
11–20–35	0.140	0.079	0.875	44
11–23–35	0.148	0.084	0.925	43
11–30–35	0.163	0.090	1.019	45
12– 1–35	0.137	0.073	0.856	47
12– 7–35	0.150	0.102	0.938	32

Kidneys (Autopsy 15054): In general there are 2 varieties of glomeruli. Most are small, lobulated, masses of lumpy hyaline material in which there are few cells, and where few patent capillaries can be found. The hyaline material is very refractive and contains lipoid deposits (Scharlach R, carbol fuchsin). Many of these hyaline masses are partially covered by a thin layer of visceral epithelium, and there are some hyaline crescents of stratified fibrillary material resembling collagen fibres. Most of the associated tubules are small, atrophied, and lie in a moderately scarred interstitium infiltrated by patches of lymphoid cells.

There are relatively few of the 2nd variety of glomeruli which are larger than the others, and contain less of the intercapillary hyaline material. The walls of some capillaries are infiltrated by hyaline material, and between capillaries there is some fibrillary, cellular, connective tissue. There is some necrosis and proliferation of both visceral and parietal epithelium in these glomeruli; and their tubules form groups which are fairly well preserved. Many are obstructed and dilated by irregular masses and rounded globules of dense hyaline material like that in the glomeruli, and there is pressure atrophy of the epithelium. There is moderate thickening of the intima of the intrarenal arteries, and a few necrotic terminal arterioles can be found.

Case 6. L. R., W.M., 20 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Onset with oedema in November, 1937, about 1 year and 9 months before death. The patient was admitted to the hospital 5 times. The disease was characterized by progressive loss of renal function and increasing hypertension. About a month after onset maximum urea clearance was 29 and 30 per cent of normal standard. There was oedema, hypertension (pressure varying from

128/77 to 165/90), plasma protein 4.05 gm. per cent, A/G ratio 40/60, and blood cholesterol 625 mg. per cent. During the next 11 months urea clearance fell to 14 and 15 per cent of normal standard, and blood N.P.N. rose from 53 to 73 mg. per cent. Eight months later the patient died in uremia. *Urine* (67 examinations): Red cells found 56 times, varying from about 1 to 300 per h.p.f. Gross haematuria occurred at times.

Urinary Proteins (11 weekly analyses, beginning about 1 year and 5 months after onset, and ending 2 months before death):

Date	P.N.	A.N.	T.P.	r.G.%
3–24–39	0.151	0.092	0.944	39
3–30–39	0.054	—	0.338	—
4– 7–39	0.046	—	0.288	—
4–15–39	0.079	0.050	0.494	37
4–20–39	0.088	0.059	0.550	33
4–27–39	0.074	0.056	0.463	24
5– 4–39	0.101	0.076	0.631	25
5–12–39	0.088	0.065	0.550	26
5–18–39	0.088	0.066	0.550	25
5–25–39	0.093	0.067	0.581	28
6– 1–39	0.089	0.050	0.556	44

Kidneys (Autopsy 16504): Most glomeruli are enlarged. Many measure from 250 to 350 μ in diameter. (Glomeruli of normal adult kidneys measure about 165 to 225 μ in Zenker fixed paraffin sections). All glomeruli contain dense hyaline material which has infiltrated and surrounded walls of capillaries, and in many tufts has formed large masses which have pushed capillaries to the periphery. Hyaline material is more abundant in some glomeruli than in others. Some portions of it contain few, others numerous nuclei. Some glomerular arterioles are infiltrated by hyaline material. There is little proliferation of epithelium.

There is moderate to marked atrophy of most cortical tubules, and there is moderate interstitial scarring, together with little patchy infiltration of lymphocytes. A few groups of tubules are obstructed and much dilated by masses of hyaline material like that in the glomeruli and there is pressure atrophy of the epithelium. The interlobar and arcuate arteries show marked, the interlobular slight thickening of intima.

Case 7. S. W., W.F. 14 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Proteinuria and oedema began in July, 1934. Examination 7 months later showed anasarca, low plasma protein (3.74 gm. per cent), inverted A/G ratio, 38/62, blood cholesterol 666 mg. per cent, and normal N.P.N. (28 to 32 mg. per cent). Urea clearance was 62 per cent of normal maximum and 71 per cent of normal standard. The phthalein excretion was 71 and 95 per cent in 2 hours. Maximum *blood pressure*, 140/90. *Urine* (17 examinations in 2 months): Doubly refractile cholesterol esters present, and red cells varying from 1 to "many" found

15 times. *Course:* During this period of 2 months protein in urine (6 analyses) varied from 0.163 to 1.350 gm. per cent, and the proportion of globulin from 3 to 18 per cent of total protein. During the next year, between June, 1935, and July, 1936, total urinary protein remained high, the proportion of globulin increased, and on 5 of 8 analyses was found to constitute from 35 to 50 per cent of the urinary protein. During this period progressive renal failure and hypertension developed. By November, 1935, the phthalein excretion was 25 per cent in 2 hours and 10 minutes. *Blood pressure* remained around 165/135 during the last 4 months. The patient died in uremia about 2 years from onset.

Urinary Proteins (14 analyses in 17 months, beginning 7 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
2–16–35	0.026	—	0.163	—
2–22–35	0.115	0.112	0.719	3
3–11–35	0.077	0.072	0.481	6
3–21–35	0.216	0.179	1.350	17
4– 6–35	0.175	0.143	1.094	18
4–12–35	0.139	0.131	0.869	6
6– 3–35	0.094	0.047	0.588	50
7–24–35	0.181	0.100	1.131	45
9–21–35	0.223	0.123	1.394	49
11–25–35	0.270	0.202	1.688	25
1–13–36	0.240	0.156	1.500	35
2–29–36	0.231	0.169	1.444	27
4–23–36	0.292	0.184	1.825	37
7–14–36	0.228	0.161	1.425	29

Kidneys (Autopsy 14918): The glomerular lesions differ in degree in various areas and in single glomeruli. Some glomeruli are almost completely converted into fibrous scar-like tissue. The rest show connective tissue cells and fibres between some capillaries, and masses of hyaline material between and around others. Some of these circumscribed masses are 50 μ in diameter. Some capillary loops are infiltrated by hyaline material. Some hyaline masses are partly covered by a single layer of epithelium. There are no crescents.

Most tubules lie atrophied in a moderately scarred interstitium infiltrated by few leucocytes. A few groups of tubules, widely dilated, are lined by large cells, some of which contain lipoid deposits, including cholesterol esters. A good many other tubules are obstructed and dilated by masses of hyaline material like that in the glomeruli. These tubules show pressure atrophy of epithelium. Rarely a tubule filled with compact threads of fibrin can be found. There are no haemorrhages. Some tubules contain leucocytes. There is practically no sclerosis of the intrarenal arteries.

Case 8. C. S., W.M. 46 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Oedema appeared in November, 1935. The patient was examined about 2 months after onset, and was in the hospital for 2½ months. He left Baltimore and further studies could not be made. Examination showed oedema, decreased

plasma protein (4.56 to 6.09 gm. per cent), inverted A/G ratio (37/63 to 34/66), normal *blood pressure* (maximum, 128/70), and N.P.N. usually between 50 and 60 mg. per cent. Urea clearance (4 tests) varied between 16 and 22 per cent of normal standard. *Urine* (72 examinations): Red cells, found 58 times, varied from about 1 to 10 per h.p.f.

Urinary Protein (10 analyses in 2 months, beginning 2 months after onset):

Date	P.N.	A.N.	T.P.	r.G.%
1– 4–36	0.160	0.076	1.000	52
1–11–36	0.207	0.127	1.294	39
1–18–36	0.154	0.076	0.963	51
1–26–36	0.138	0.081	0.863	41
2– 1–36	0.167	0.092	1.044	45
2– 8–36	0.180	0.103	1.125	43
2–15–36	0.149	0.103	0.931	31
2–21–36	0.138	0.084	0.863	39
2–29–36	0.177	0.116	1.106	34
3– 7–36	0.203	0.117	1.269	42

Case 9. S. K., C.F. 16 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* In January, 1939, at the time of an appendectomy, urine was positive for "albumin." *Blood pressure* was 130/75. Oedema of legs appeared 9 months later. Examinations in January, 1940, showed anasarca, proteinuria, low plasma protein, microscopical haematuria, elevated blood cholesterol (536 mg. per cent), blood N.P.N. of 26 mg. per cent, and slight hypertension (140/90). *Course:* During the next 9 months massive proteinuria, low plasma protein, and oedema persisted. Blood cholesterol usually around 600 mg. per cent. Blood pressure varied, usually from 110/80 to 150/110. The proportion of globulin in blood plasma usually varied between 60 and 77 per cent of the total protein. The proportion of globulin in urinary protein was nearly always high. Urea clearance, at first 67 and 46 per cent of normal standard, fell in 8 months to 11.5 and 11.5 per cent of normal standard. The blood N.P.N. rose to 60 mg. per cent. During last four months urea clearance fell to 3 per cent of normal standard. Blood N.P.N. rose to 176 mg. per cent. Blood cholesterol fell to normal. Concentration of protein in urine diminished. There was no marked change in blood pressure. It varied from 197/138 to 120/82. *Urine* (182 examinations): Red cells found 181 times, varying from about 1 to 50 per h.p.f.

Urinary Proteins (55 analyses in 13 months, beginning about 3 months after onset of oedema):

Date	P.N.	A.N.	T.P.	r.G.%
1–20–40	0.274	0.200	1.713	28
1–27–40	0.173	0.131	1.081	24
2– 3–40	0.183	0.129	1.144	30
2–10–40	0.343	0.227	2.144	34
2–17–40	0.117	0.072	0.731	38
2–24–40	0.182	0.120	1.138	34
3– 2–40	0.239	0.162	1.494	32

Date	P.N.	A.N.	T.P.	r.G.%
3– 9–40	0.233	0.150	1.456	36
3–16–40	0.212	0.147	1.325	31
3–24–40	0.306	0.219	1.913	28
3–30–40	0.187	0.130	1.169	30
4– 7–40	0.203	0.129	1.269	36
4–13–40	0.266	0.179	1.663	33
4–20–40	0.197	0.134	1.231	32
4–27–40	0.209	0.149	1.306	29
5– 4–40	0.359	0.251	2.244	30
5–11–40	0.341	0.220	2.131	35
5–18–40	0.157	0.103	0.981	34
5–26–40	0.302	0.214	1.888	29
6– 2–40	0.258	0.173	1.613	33
6–10–40	0.256	0.169	1.600	34
6–16–40	0.378	0.259	2.363	31
6–23–40	0.340	0.254	2.125	25
7– 2–40	0.266	0.157	1.663	41
7– 7–40	0.235	0.131	1.469	44
8– 9–40	0.303	0.157	1.894	47
8–14–40	0.246	0.145	1.538	41
8–18–40	0.168	0.080	1.050	52
8–24–40	0.173	0.101	1.081	42
9– 1–40	0.194	0.105	1.213	46
9– 8–40	0.194	0.103	1.213	47
9–16–40	0.074	0.039	0.463	47
9–22–40	0.256	0.129	1.600	50
9–29–40	0.225	0.124	1.406	45
10– 6–40	0.218	0.108	1.363	50
10–13–40	0.209	0.112	1.306	46
10–20–40	0.245	0.129	1.531	47
10–27–40	0.204	0.116	1.275	42
11– 3–40	0.221	0.122	1.381	40
11–10–40	0.151	0.092	0.944	40
11–17–40	0.123	0.073	0.769	41
11–24–40	0.098	0.160	1.000	39
12– 1–40	0.088	0.054	0.550	39
12–10–40	0.102	0.070	0.638	31
12–15–40	0.121	0.077	0.756	36
12–22–40	0.081	0.050	0.506	38
12–28–40	0.102	0.064	0.638	37
1– 5–41	0.220	0.146	1.375	34
1–12–41	0.084	0.053	0.525	37
1–19–41	0.094	0.058	0.588	38
1–26–41	0.069	0.045	0.431	35
2– 2–41	0.124	0.075	0.775	40
2– 9–41	0.117	0.079	0.731	32
2–16–41	0.103	0.061	0.644	41
2–23–41	0.099	0.060	0.619	39

Kidneys (Autopsy 17311): All glomeruli show changes of the same kind, differing in degree. Some are moderately enlarged, and there is necrosis and proliferation of epithelium in many. Few crescents are found. All glomeruli show two varieties of intercapillary material. Some is hyaline, but fibrillary in appearance, and is associated with nuclei. The other variety is hyaline, and homogeneous. It contains no nuclei and is distributed between capillaries in various forms. There are rounded masses, many 30 to 40 μ in diameter, larger irregular masses, and many narrow, branching and confluent stream-like accumulations. Many of these, in frozen sections, give positive staining reactions for fat. Some of the lipoid material consists of fluid crystals of cholesterol esters. These hyaline coagula look and stain like the casts in tubules.

Many tubules are atrophied and lie in a scarred interstitial tissue irregularly infiltrated by few lymphocytes. Many other patches of tubules show extreme dilatation by coagula of homogeneous hyaline material alone or together with polymorphonuclear leucocytes, many of them necrotic. In tubules as in glomeruli some of the hyaline material contains lipoids (Scharlach R). There are similar lipoids in foci of renal epithelium.

Occasional interlobar arteries show patches of thickened intima. There is little intimal thickening of small interlobular arteries. Few hyaline terminal arterioles can be found. There are fresh haemorrhages in few tubules.

Case 10. H. G., C.M. 21 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Onset of anasarca, nocturia, frequent urination about July 1, 1940. Examination three months later showed anasarca, retinal exudates, low plasma protein, urea clearance 50 per cent of normal maximum, 29 per cent of normal standard, and hypertension. *Course:* During a month in hospital *blood pressure* varied usually between 190/140 and 270/150. Blood cholesterol was 419 mg. per cent. Blood N.P.N. rose from 42 to 116 mg. per cent. Death occurred about five months after onset of oedema. *Urine* (17 examinations): Red cells, always found, varied from occasional to about 100 per h.p.f. Crystals of cholesterol esters also found.

Urinary Proteins (4 analyses during last 3 weeks of the disease):

Date	P.N.	A.N.	T.P.	r.G.%
10–18–40	0.128	0.066	0.800	48
10–27–40	0.111	0.059	0.694	47
11– 3–40	0.116	0.054	0.725	53
11– 5–40	0.155	0.086	0.969	44

Kidneys (Autopsy 17141): Some glomeruli are small and completely hyaline. Most are enlarged and capillaries are thickened, infiltrated and surrounded by dense hyaline material which is also found between some capillary loops in the form of irregular masses and globules. There are a good many nuclei embedded in the hyaline material. Many glomeruli contain epithelial crescents. There is some necrosis and regeneration of visceral epithelium.

Most tubules are atrophic. The interstitial tissue is moderately scarred, in places infiltrated by moderate numbers of lymphocytes. Many other tubules are widely distended by dense hyaline material. A few contain clots of fibrin without any red cells. Few are filled with blood. There are a few scattered groups of tubules of normal size. Some are lined by and their lumina contain desquamated epithelial cells in which there are many doubly refractive fluid crystals of cholesterol esters.

There is slight to moderate thickening of intima of the intrarenal arteries by cellular connective tissue. Many terminal arterioles are narrowed and hyaline. Some are necrotic.

GROUP 5

Case 1. A. D., W.F. 15 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Oedema of legs in February, 1936, was the 1st sign. During the next 4½ years, oedema was of slight degree. *Blood pressure* was elevated at times (maximum, 158/90 and 140/105). Blood cholesterol (1 determination) was 355 mg. per cent. The lowest plasma protein was 3.5 gm. per cent; lowest A/G ratio, 48/52. Renal failure progressed slowly, and function changed little between 1936 and 1938. Urea clearance in 1936 (7 tests) varied between 23 and 49 per cent of normal standard, and between 30 and 36 per cent of normal maximum. In 1938, (1 test) the clearance was 23 per cent of normal standard and 28 per cent of normal maximum. In June, 1940, about 4½ years after onset, urea clearance was 6.7 and 16 per cent of normal maximum. Blood pressure was 152/98. *Urine* (81 examinations): Red cells always found, varying from about 10 to 80 per h.p.f.

Urinary Proteins (10 analyses in 1936, beginning 1 month after the onset, and 2 in 1940):

Date	P.N.	A.N.	T.P.	r.G.%
3- 9-36	0.043	—	0.269	—
3-14-36	0.062	—	0.388	—
3-24-36	0.084	0.052	0.525	38
3-28-36	0.060	—	0.375	—
4- 4-36	0.039	—	0.244	—
4-11-36	0.078	0.054	0.488	31
4-18-36	0.094	0.040	0.588	57
4-25-36	0.061	—	0.381	—
5- 2-36	0.078	0.056	0.488	28
6-30-36	0.060	—	0.375	—
6- 2-40	0.030	—	0.188	—
6- 9-40	0.026	—	0.163	—

Case 2. T. G., C.M. 7 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Onset of anasarca in January, 1933. During the next 5½ years pneumococcal septicaemia and peritonitis occurred 5 times. *Blood pressure* was elevated at times, over 200 on last admission. *Blood:* Plasma protein usually low (3.4 to

5.75 gm. per cent) and A/G ratio inverted (46/54 to 29/71). Plasma cholesterol was often high. The maximum, 857 mg. per cent. *Renal function* not tested by urea clearance until late in the disease. Blood N.P.N. was elevated at times and normal at times. The peaks of elevated N.P.N. increased. The child died with peritonitis, uremia, and hypertension. *Urine* (269 examinations): Red cells varying from 1 to "innumerable" per h.p.f. found 214 times. Fluid crystals of cholesterol esters present.

Urinary Proteins (23 analyses in 2 years, beginning 9 months after the onset and ending 1 year and 7 months before death):

Date	P.N.	A.N.	T.P.	r.G.%
10- 6-34	0.132	0.074	0.825	44
10-12-34	0.063	—	0.394	—
2- 9-35	0.073	0.062	0.456	15
2-29-36	0.080	0.059	0.500	26
3- 2-36	0.017	—	0.106	—
3- 7-36	0.033	—	0.206	—
3-14-36	0.050	—	0.313	—
3-21-36	0.051	—	0.319	—
3-27-36	0.102	0.067	0.638	34
6-16-36	0.057	—	0.356	—
6-23-36	0.109	0.070	0.681	36
6-30-36	0.082	0.049	0.513	40
7- 7-36	0.064	0.039	0.400	39
7-14-36	0.078	0.054	0.488	31
7-21-36	0.091	0.077	0.569	15
8- 4-36	0.098	0.076	0.613	22
8-18-36	0.057	—	0.356	—
9- 1-36	0.081	0.075	0.506	7
9-16-36	0.099	0.084	0.619	15
9-30-36	0.129	0.104	0.806	19
10-21-36	0.144	0.122	0.900	15
10-28-36	0.125	0.099	0.781	21
11-12-36	0.160	0.121	1.000	24

Kidneys (Autopsy 15890): There are moderate numbers of completely hyaline glomeruli and groups of extremely atrophied tubules in scarred interstitial tissue infiltrated with lymphoid cells. Most glomeruli are enlarged and show varying amounts of hyaline material surrounding open capillaries, infiltrating their walls, and lying between them. There is some increase in cells between capillaries and there are a few epithelial and fibrous crescents.

Most tubules are considerably atrophied, with a good deal of interstitial scar tissue between them. There is hyaline material and calcified material in few tubules. A few patches of tubules show swollen epithelium filled with lipoids, including cholesterol esters. There is slight to moderate thickening of intima of the intrarenal arteries and arterioles.

Case 3. F. M., W.F. 12 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* The first sign was oedema, in October, 1930. The patient was examined a month later, and many times during the next 9½ years. *Blood pressure* was normal at times, elevated at times and was as high as 150/100 in 1930. *Blood:* Plasma protein varied from 3.17 to 5.62 gm. per cent; A/G ratio from 58/42 to 36/64. *Renal Function:* From 1930 to the end of November, 1936 urea clearance, determined many times, was usually around 75 per cent of normal maximum. When first examined after 1936, in March, 1939, it was 10.5 per cent of normal standard. Blood N.P.N. was 55 mg. per cent. Blood pressure, 155/105. She was not seen again, and died May 22, 1940. There was no autopsy. *Urine:* Red cells found on 291 of 320 examinations, varied from 1 to about 200 per h.p.f. Gross haematuria occurred several times.

Urinary Proteins (41 analyses in 13 months, beginning 5 years after onset of symptoms and ending 3½ years before death):

Date	P.N.	A.N.	T.P.	r.G.%
10–17–35	0.042	—	0.263	—
10–26–35	0.112	0.090	0.700	20
11– 2–35	0.036	—	0.225	—
11–29–35	0.125	0.122	0.781	2
12– 4–35	0.087	0.084	0.544	3
12–11–35	0.154	0.142	0.963	8
12–18–35	0.113	0.103	0.706	9
12–25–35	0.198	0.172	1.238	13
1– 1–36	0.147	0.131	0.919	11
1– 8–36	0.079	0.077	0.494	3
1–15–36	0.187	0.161	1.169	14
1–23–36	0.195	0.154	1.219	21
1–26–36	0.037	—	0.231	—
1–29–36	0.071	0.051	0.444	28
2– 1–36	0.145	0.105	0.906	28
2– 5–36	0.072	0.068	0.450	6
2– 8–36	0.090	0.055	0.563	39
2–15–36	0.142	0.104	0.888	27
3– 5–36	0.155	0.145	0.969	6
3–11–36	0.164	0.134	1.025	18
3–18–36	0.147	0.124	0.919	16
3–25–36	0.156	0.138	0.975	11
4– 1–36	0.133	0.104	0.831	22
4– 8–36	0.181	0.148	1.131	18
4–15–36	0.145	0.114	0.906	21
4–22–36	0.114	0.076	0.713	32
4–28–36	0.117	0.092	0.731	21
5– 5–36	0.100	0.080	0.625	20
5–12–36	0.068	0.058	0.425	15
5–19–36	0.125	0.110	0.781	12
5–26–36	0.117	0.107	0.731	9

Date	P.N.	A.N.	T.P.	r.G.%
6–30–36	0.168	0.126	1.050	25
8– 4–36	0.123	0.099	0.769	20
8–18–36	0.164	0.139	1.025	16
9– 1–36	0.113	0.096	0.706	15
9–16–36	0.082	0.075	0.513	9
9–30–36	0.102	0.083	0.638	19
10–14–36	0.088	0.077	0.550	13
10–28–36	0.110	0.079	0.688	28
11–12–35	0.110	0.092	0.687	16
11–25–36	0.131	0.102	0.819	22

Case 4. M. M., W.F. 17 months old. *Diagnosis:* Lipoid nephrosis. *History:* The disease began with oedema in January, 1934. For six weeks there was oliguria, increasing oedema and some elevation of *blood pressure.* Thereafter the pressure was usually normal. *Blood:* Plasma protein varied from 2.3 to 5.7 gm. per cent; A/G ratio from 72/28 to 44/56. Blood N.P.N. varied from 33 to 44; cholesterol from 612 to 1140 mg. per cent. *Course:* Pneumococcus, type 19, septicaemia and peritonitis developed nearly two years after onset of symptoms, and the child died. *Urine* (64 examinations): Red cells, found 31 times, varied from "rare" to about 10 per h.p.f. Fluid crystals of cholesterol were found.

Urinary Proteins (4 analyses during the last 16 days of the disease):

Date	P.N.	A.N.	T.P.	r.G.%
11–13–35	0.204	0.180	1.275	12
11–19–35	0.279	0.228	1.744	18
11–23–35	0.251	0.206	1.569	18
11–28–35	0.264	0.148	1.650	44

Kidneys (Autopsy 14537): There is no distortion of architecture, interstitial scarring or wide dilatation of tubules. Arteries and arterioles are normal. In each cortical labyrinth a few tubules show slight atrophy of epithelium. In many cells of convoluted tubules are lipoid deposits, including crystals of cholesterol esters. Most glomeruli are normal. There are rare completely hyaline small glomeruli. In few glomeruli there are very small focal collections of homogeneous hyaline material which completely surrounds occasional single capillary loops, and is deposited in the form of small masses between loops of capillaries. These measure from 4 to 24μ in diameter. There is similar hyaline material in a few widened tubules with somewhat atrophied epithelial lining.

GROUP 6

Case 1. A. S., C.F. of 42 years. *Diagnosis:* Chronic hypertension; dissecting aortic aneurysm; intrarenal arteriosclerosis; acute arteriolonecrotic nephritis. *History:* Dyspnoea and hypertension for 3 years. Pain in chest about 6 weeks before death. *Course: Blood pressure* was high, 220/125 to 280/184. At first there was a trace of protein in urine. In about 4 weeks, proteinuria increased to several grams per liter. Blood N.P.N. rose from 26 to 172 mg. per cent.

Urinary Proteins (3 analyses during the last week of the disease, when blood N.P.N. was 88 to 172 mgms. per cent):

Date	P.N.	A.N.	T.P.	r.G.%
7–24–35	0.052	—	0.325	—
7–25–35	0.048	—	0.300	—
7–29–35	0.062	—	0.388	—

Kidneys (Autopsy 14343): The intrarenal arteries, especially the interlobular vessels, are greatly narrowed by thickening of the intima. Many terminal arterioles are hyaline and narrow. Many are necrotic. There are small scattered superficial areas of necrotic tissue, and scattered glomeruli show necrotic capillary loops, necrotic, swollen, and proliferating epithelium. Most glomeruli, however, are atrophic. Most tubular epithelium is extremely vacuolated. There are a few old lesions, in the form of small foci of atrophied tubules and hyalinized glomeruli.

Case 2. W. W., C.M. 45 years old. *Diagnosis:* Chronic hypertension; arterio- and arteriolosclerotic nephritis. *History:* Shortness of breath and dizziness for about 7 months. Headache and vomiting for about 2 months. *Course:* During a period of about 2 weeks in hospital, *blood pressure* varied from 196/120 to 285/140. The patient was in uremia. Blood N.P.N. rose from 92 to 196 mg. per cent.

Urinary Proteins (3 analyses during the last week of the disease, when the blood N.P.N. was 196 mg. per cent):

Date	P.N.	A.N.	T.P.	r.G.%
12–28–35	0.043	—	0.269	—
1– 1–36	0.057	—	0.356	—
1– 2–36	0.038	—	0.238	—

Kidneys (Autopsy 14584): There is marked sclerosis of intrarenal arteries. The interlobulars are much narrowed. Many terminal arterioles are hyaline. Some are necrotic.

Changes in the renal tissue are patchy. There are many foci of atrophied tubules and glomeruli, hyalinized glomeruli, and scarred interstitial tissue infiltrated with moderate numbers of lymphocytes. These areas alternate with others where tubules are fairly well preserved, glomeruli are large, and interstitial tissue is nearly normal. Some arterioles in these areas are necrotic, and some glomeruli show necrotic segments, thrombi in capillaries, proliferating epithelium, and fibrin clots between tufts of capillaries. A few tubules are dilated, filled with hyaline material.

Case 3. B. R., C.M. 46 years old. *Diagnosis:* Chronic pyelonephritis, arteriosclerotic nephritis, and hypertension. *History:* Dyspnoea and swollen ankles for 2 years. Vomiting for 4 months. The patient was in uremia. *Blood pressure,*

154/110. During the next month, until death, the condition was essentially unchanged.

Urinary Proteins (5 analyses in 13 days, when blood N.P.N. was 196 and 216 mg. per cent):

Date	P.N.	A.N.	T.P.	r.G.%
9– 9–35	0.041	—	0.256	—
9–12–35	0.028	—	0.175	—
9–15–35	0.022	—	0.138	—
9–18–35	0.034	—	0.213	—
9–21–35	0.034	—	0.213	—

Kidneys (Autopsy 14435): There is widespread, nearly diffuse chronic inflammation and scarring of interstitial tissue. Most glomeruli are small and hyaline, and the tubules atrophied. Many tubules form small rounded channels filled with colloid-like material. There are a few small scattered areas where glomeruli are larger, partly hyalinized, and tubules are more nearly normal. Some contain purulent exudate. There is necrosis and proliferation of epithelium in many of the better preserved glomeruli. The intrarenal arteries show marked thickening of intima. There are many hyaline arterioles.

Case 4. V. D., W.F. 12 years old. *Diagnosis:* Chronic nephrotic nephritis. *History:* Onset of oedema, headache, and vomiting in 1931. The urine contained much protein, casts and many red cells. Blood N.P.N. was 28 and cholesterol 607 mg. per cent. *Course:* During the next four years signs and symptoms varied. The plasma protein rose, and the A/G ratio varied from 33/67 to 59/41. *Blood pressure* was normal at times and elevated at times, the highest 150/110. Four years after onset the patient died in uremia.

Urinary Proteins (8 analyses in the last 2½ months of the disease, when blood N.P.N. varied from 124 to 224 mg. per cent):

Date	P.N.	A.N.	T.P.	r.G.%
3–25–35	0.069	0.059	0.431	14
3–31–35	0.078	0.055	0.488	29
4– 9–35	0.071	0.061	0.444	14
4–12–35	0.064	0.060	0.400	6
4–19–35	0.058	—	0.363	—
5–11–35	0.053	—	0.331	—
5–23–35	0.113	0.060	0.706	47
6– 1–35	0.052	—	0.325	—

Kidneys (Autopsy 14262): Most glomeruli are very small, completely hyalinized. Tubules are extremely atrophied. Interstitial tissue is scarred. There are a few small foci near the surface composed of wide tubules with well-preserved epithelium, normal interstitial tissue, and large glomeruli in which there is hyaline material between capillaries, necrotic, swollen and regenerating epithelium, and tortuous arterioles with hyaline areas.

Case 5. R. L., C.M. 7 years old. *Diagnosis:* Chronic cystitis, pyelitis, and pyelonephritis; arteriolosclerotic nephritis, chronic hypertension. *History:* Frequency of urination and slight proteinuria from the age of 2 to 5 years. Hypertension discovered when child was 5 years old. *Blood pressure,* 130/90 to 184/160. Blood N.P.N., 71 mg. per cent. *Course:* During the next 2 years hypertension persisted (maximum, 202/136), renal insufficiency progressed, and the child died in uremia at least 5 years after first signs of disease.

Urinary Proteins (7 analyses during last 3 months of the disease when blood N.P.N. ranged between 84 and 206 mg. per cent):

Date	P.N.	A.N.	T.P.	r.G.%
11–15–35	0.012	—	0.075	—
11–19–35	0.021	—	0.131	—
11–23–35	0.019	—	0.119	—
11–30–35	0.016	—	0.100	—
1–30–36	0.043	—	0.269	—
2– 1–36	0.041	—	0.256	—
2– 5–36	0.040	—	0.250	—

Kidneys (Autopsy 14644): Most of the cortex consists of dense scarred interstitial tissue with small hyaline glomeruli, extremely atrophied tubules, and foci of lymphocytes. There are areas of better preserved tissue showing relatively little interstitial scar, and large tubules. The small interlobular arteries in these areas show moderate thickening of intima. There are hyaline areas in some terminal arterioles. A few are necrotic. Glomeruli in these areas are larger than normal. Some contain epithelial crescents, and in most there is necrosis and proliferation of visceral epithelium. Between capillaries are variable numbers of connective tissue cells and fibers. In some glomeruli are small amounts of hyaline material between capillary loops. Some tubules contain hyaline material. In some are clots of fibrin. The renal pelvic tissue is very thick, densely infiltrated with lymphocytes.

Case 6. I. S., W.F. 24 years old. *Diagnosis:* Chronic nephrotic nephritis, chronic pyelitis and pyelonephritis; arterio- and arteriolosclerotic nephritis. *History:* Onset in 1925 with oedema. Subsequent examinations showed marked proteinuria, gross haematuria at times, and moderate hypertension (136/84 to 155/110). During the next 10 years signs and symptoms varied. Plasma proteins were low at times, A/G ratio inverted, and cholesterol elevated (536 mg. per cent). Loss of renal function progressed slowly, and the patient died in uremia ten years after onset. During the last year of disease there was increased hypertension (maximum 250/160).

Urinary Proteins (11 analyses during the last 2 months of the disease, when blood N.P.N. was usually between 59 and 165 mg. per cent, urea clearance between 19.5 and 10 per cent of normal standard):

Date	P.N.	A.N.	T.P.	r.G.%
11- 5-35	0.060	—	0.375	—
11-29-35	0.029	—	0.181	—
12- 4-35	0.038	—	0.238	—
12-11-35	0.042	—	0.263	—
12-14-35	0.048	—	0.300	—
12-18-35	0.034	—	0.212	—
12-21-35	0.023	—	0.144	—
12-28-35	0.024	—	0.150	—
1- 4-36	0.033	—	0.206	—
1- 6-36	0.029	—	0.181	—
1- 9-36	0.036	—	0.225	—

Kidneys (Autopsy 14595): Most glomeruli are small and almost completely hyalinized. The majority of tubules are extremely atrophied. There is marked interstitial scarring. There are focal collections of monocytes filled with lipoids, including cholesterol esters, in the interstitial tissue. In the superficial cortex are a few small areas of well preserved tubules, hyaline and necrotic arterioles, and glomeruli which are large, cellular, and contain hyaline material around and between capillaries, and in capillary walls. In some glomeruli there are necrotic loops.

There is marked chronic inflammation of the pelves. In the deeper parts of the cortex and in pyramids are patches infiltrated by many lymphocytes. Some collecting tubules contain purulent exudate. The interlobular arteries show moderate to marked thickening of intima.

Case 7. F. B., W.M. 17 years old. *Diagnosis:* Chronic nephrotic nephritis and chronic pyelonephritis. *History:* Oedema of face appeared in July, 1937. Four months later, there was moderate hypertension (140/80 to 160/90), oedema, proteinuria, haematuria and impaired renal function. Urea clearance was 26 and 44 per cent of normal standard. Blood N.P.N. varied from 40 to 52. Blood cholesterol was 455 mg. per cent. *Course:* During the next two years hypertension increased, renal function decreased, and at times there were many leucocytes in the urine. The patient died in uremia 2.5 years after onset.

Urinary Proteins (24 analyses during the last 9 months of the disease, when blood N.P.N. usually ranged between 112 and 400 mg. per cent, and urea clearance between 18 and 4 per cent of normal standard):

Date	P.N.	A.N.	T.P.	r.G.%
5-12-39	0.032	—	0.200	—
5-18-39	0.041	—	0.256	—
5-25-39	0.050	—	0.313	—
6- 1-39	0.057	—	0.356	—
6- 8-39	0.073	0.053	0.456	27
9-23-39	0.064	0.044	0.400	31
9-30-39	0.086	0.060	0.538	30

Date	P.N.	A.N.	T.P.	r.G.%
10- 7-39	0.066	0.057	0.413	14
10-14-39	0.064	0.044	0.400	31
10-21-39	0.055	—	0.344	—
10-28-39	0.047	—	0.294	—
11- 4-39	0.040	—	0.250	—
11-11-39	0.039	—	0.244	—
11-18-39	0.042	—	0.263	—
11-25-39	0.044	—	0.275	—
12- 2-39	0.045	—	0.281	—
12- 9-39	0.022	—	0.138	—
12-16-39	0.021	—	0.131	—
12-31-39	0.024	—	0.150	—
1- 6-40	0.183	0.172	1.144	6
1-15-40	0.014	—	0.088	—
1-20-40	0.012	—	0.075	—
1-27-40	0.014	—	0.088	—
2- 3-40	0.041	—	0.256	—

Kidneys (Autopsy 16777): Many glomeruli are almost completely hyalinized and there are many hyaline crescents. Most tubules are extremely atrophied. The interstitial tissue is scarred and infiltrated with many lymphocytes and some polymorphonuclear leucocytes (one or two small abscesses were found in the kidneys, and in the prostate). Scattered near the cortical surfaces are small foci of fairly well preserved tubules and large glomeruli which are cellular and contain hyaline material which infiltrates capillary walls and lies in the form of irregular masses between capillaries. The intrarenal arteries are tortuous and there is slight thickening of intima of some. A few hyaline arterioles can be found.

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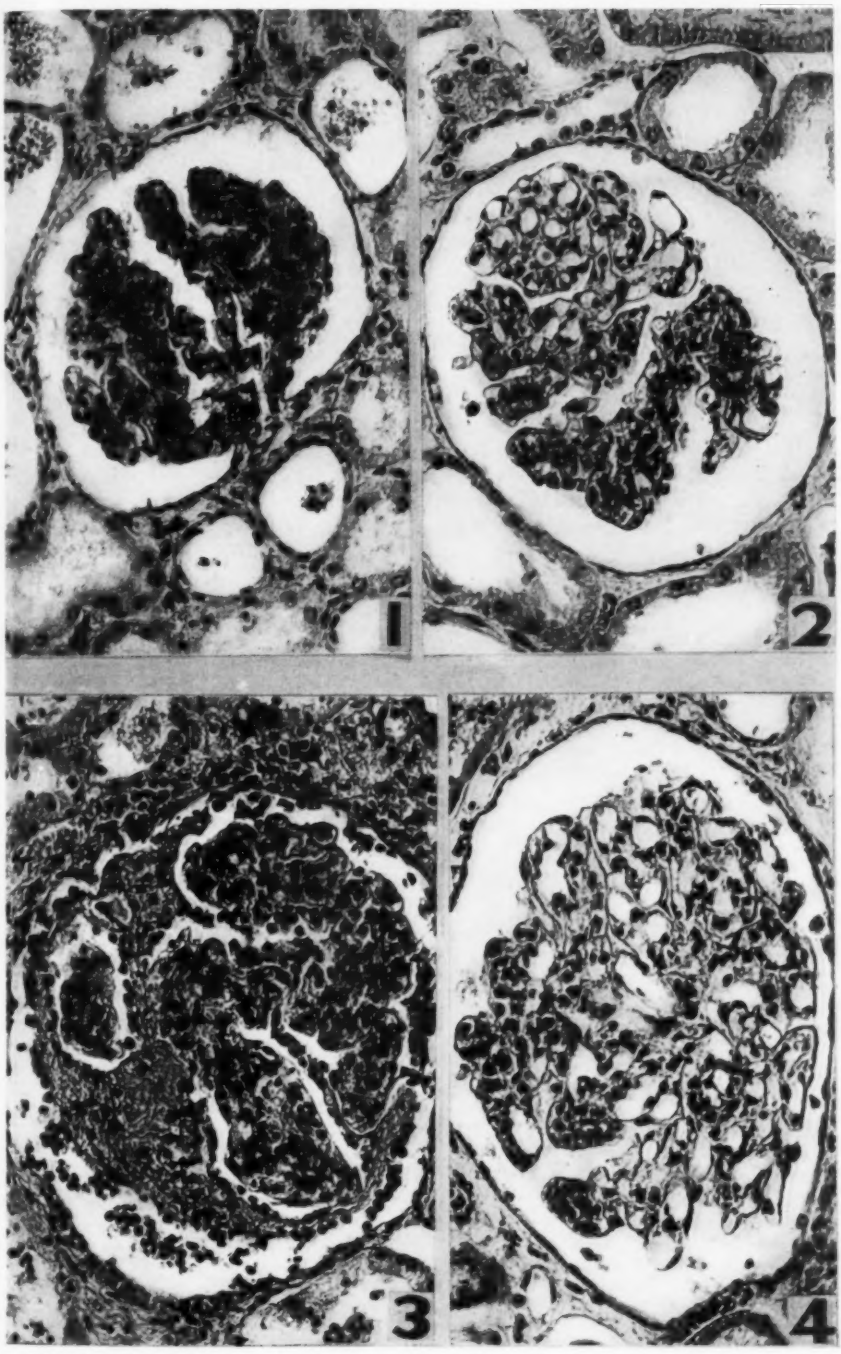
PLATE 1

FIGURES 1 and 2. *Group 1, Case 7.* Acute haemorrhagic nephritis.

Proteinuria of low concentration. No coagula developed in the kidney. *Figure 1:* A typical glomerulus which looks solid and cellular. *Figure 2:* A glomerulus from the perfused kidney. The cellular character of the glomeruli is due chiefly to leucocytes in the capillaries. The number of fixed endothelial cells is normal. (× 375)

FIGURES 3 and 4. *Group 2, Case 2.* Acute haemorrhagic nephritis.

Proteinuria of high concentration, over 40 per cent globulin. Clots of fibrinous exudate in Bowman's space in many glomeruli. Many leucocytes in the capillaries. *Figure 4:* Perfusion has washed out the leucocytes, leaving the endothelial cells plainly visible, normal in number. (× 375)



The sections illustrated in this and the following plates were stained with haematoxylin and eosin. Photographs by Mr. Milton Kougl.

PLATE 2

FIGURE 1. *Group 5, Case 2.* Chronic nephrotic nephritis, 5½ years in duration. Proteinuria was variable (0.106 to 1.000 gram per cent). High globulinuria at times. *Figure 1:* Capillaries infiltrated and surrounded by a fairly thick layer of hyaline material, and a small epithelial crescent. Kidney not perfused. (× 325)

FIGURE 2. *Group 5, Case 4.* Lipoid nephrosis, about 2 years in duration. High magnification (× 700) of part of a glomerulus (not perfused) to show the focal accumulation of a thick hyaline coagulum about a single capillary loop.

FIGURE 3. *Group 4, Case 6.* Chronic nephrotic nephritis of about 2 years duration. A representative glomerulus containing many large intercapillary masses of hyaline coagulum. The urine, examined late in the course of the disease, contained total protein and globulin in high concentration fairly often. Much of the exudate between the capillaries probably collected early in the disease. (× 390)

FIGURE 4. *Group 4, Case 7.* Chronic nephrotic nephritis of 2 years duration. Most of the glomerulus is occupied by a cellular and fibrillary material. At the right there is a circumscribed mass of homogeneous hyaline coagulum which contains lipoids (Scharlach R). (× 400)

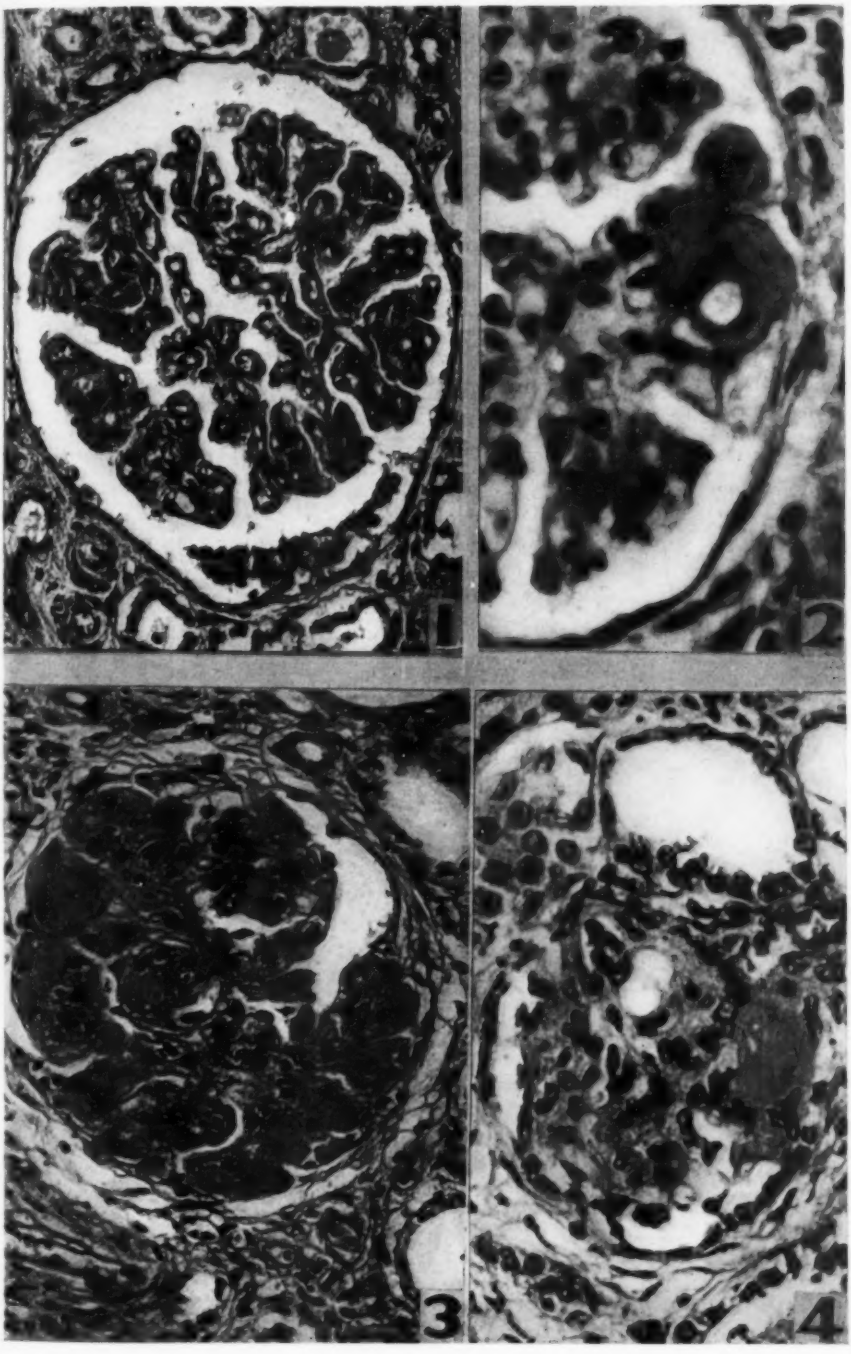

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PLATE 3

FIGURES 1, 2 and 3. *Group 4, Case 9.* Chronic nephrotic nephritis. Figures 1 and 2 (× 390) show cells, fibrillary material, and homogeneous masses of hyaline material in the glomeruli. The hyaline masses contain lipoids. The glomerulus in Figure 2 has been perfused, and the intercapillary position of the exudate is brought out. Figure 3 (× 75): obstruction and extreme distension of many tubules by coagulated exudate. The urine nearly always contained total protein and globulin in high concentration.

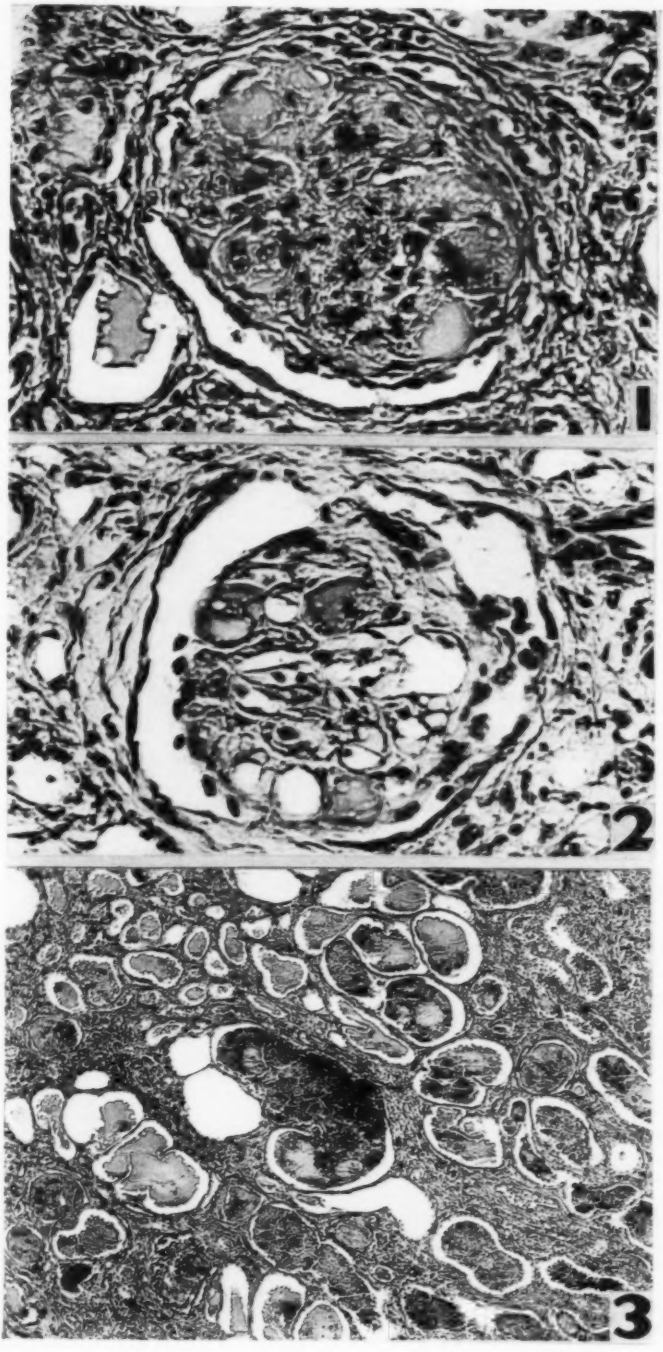
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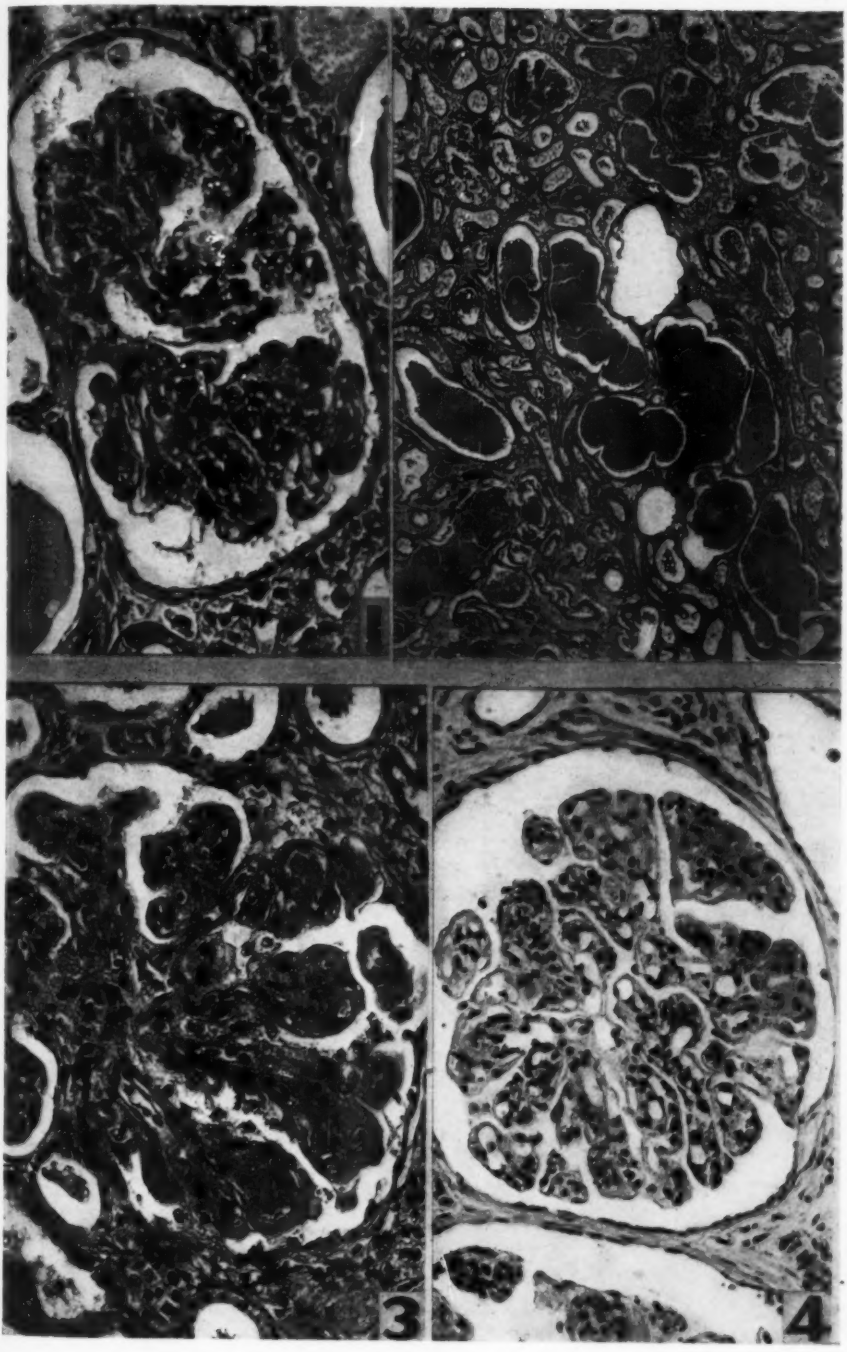
PLATE 4

FIGURES 1 and 2. *Group 4, Case 4.* Nephrotic nephritis of short duration (9 weeks). The urine contained total protein and globulin in high concentration. The patient died in uremia 9 weeks from the onset. Figure 1 (× 390) shows a glomerulus which is almost precisely like all of the others. The changes are slight. Some epithelial cells are swollen, and there are some cells in and between capillaries, but there is little exudate. Many tubules (Figure 2, × 75) are obstructed and distended by coagulated exudate.

FIGURES 3 and 4. *Group 4, Case 2.* Nephrotic nephritis, about 9 months in duration. The urine, examined once, contained protein in extremely high concentration (3.481 grams per cent), 42 per cent of it globulin. Most glomeruli were greatly enlarged due to the accumulation of hyaline material, shown in Figure 3 (× 300). The absence of proliferating endothelial cells, and the intercapillary position of the hyaline exudate is shown in Figure 4 (× 275, kidney perfused).



UNIV. OF MICH.

MYASTHENIA GRAVIS COMPLICATED BY THYROTOXICOSIS: CREATINE STUDIES

Case Report

GEORGE W. THORN AND NICHOLAS A. TIERNEY

From the Chemical Division, Medical Clinic, The Johns Hopkins University and Hospital

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The coexistence of myasthenia gravis and thryotoxicosis is extremely rare (1, 2, 3, 4, 5) although muscular atrophy and myasthenia are observed frequently in patients with thyrotoxicosis (6, 7, 8). This report presents an instance (Patient N. G.) of the rare combination of the two diseases. In this case, a study of the effect of iodine therapy on creatine metabolism proved to be extremely helpful in estimating the improvement in muscular function which might follow sub-total thyroidectomy.

Spontaneous creatinuria and a marked decrease in tolerance to administered creatine have been observed in patients with thyrotoxicosis (9, 10) as well as in patients with myasthenia gravis (11). It has been observed that iodine therapy greatly reduces the creatinuria and increases the creatine tolerance of patients with thyrotoxicosis (9, 10) whereas Milhorat *et al.* (11) have reported that iodine therapy was without effect on the creatine output of a patient with myasthenia gravis.

METHODS

The patient was studied on the Metabolism Ward of The Johns Hopkins Hospital where she was provided with a diet low in creatine. The diet contained sufficient calories and protein to meet metabolic requirements. Daily creatine and creatinine determinations were made on 24-hour urine specimens which were collected under toluene and kept cold. Preformed and total creatinine were determined according to the method of Folin (12).

Creatine tolerance tests were performed as follows: On the morning of the test, following a period of 2–5 days during which the patient had been maintained on a diet of low creatine content, 2.64 gm. of creatine, dissolved in 400 cc. of water, was administered orally prior to breakfast. The excretion of creatine and cre-

atinine was followed during the subsequent 24-hour period. The test dose of creatine, 2.64 gm. (Eimer and Amend glycocyamine containing one molecule of water) is equivalent to 2.0 gm. of creatine in the urine expressed as creatinine. The per cent of creatine excreted was calculated by subtracting from the total amount of creatine excreted on the test day, the amount excreted spontaneously on the day previous to the test. This latter figure when divided by the total amount of creatine which might have been excreted (2.0 gm.) represents the per cent excreted. In each instance the urine was tested for the presence of acetone or diacetic acid. Maximum normal values for the excretion of creatine are 20 per cent for men and 30 per cent for women.

Changes in muscular response were followed by testing the patient's ability to raise a column of mercury by blowing through a tube attached to a flask with a glass tube inlet and outlet, the latter being connected with a No. 20 hypodermic needle which in turn was connected with a mercury manometer.

PROTOCOL

N. G. (No. 143931), a negro school teacher, 45 years of age, was admitted to The Johns Hopkins Hospital on February 5, 1929, complaining of double-vision and drooping of both eyelids. Her illness had begun in November, 1928 when she first noticed drooping of the eyelids and inability to move her eyes. Her family history was noncontributory.

Physical examination on admission, February 5, 1929, revealed a thin, rather poorly nourished, colored woman. Her temperature was 99°F., pulse 122, respirations 24, and blood pressure 150/70 mm. of Hg. Her skin was moist and pale. There was marked ptosis of both eyelids, left external strabismus, bilateral exophthalmos and tremor of the tongue. The thyroid was not enlarged; however a bruit was audible over the gland. Examination of the heart revealed slight enlargement. The heart sounds were of good intensity, the first sound over the mitral area being accentuated. At the apex a presystolic rumble as well as a systolic murmur could be heard. Initial contraction of the skeletal muscles was strong but they fatigued easily.

The laboratory data on this admission were as follows: R.B.C. 4.29 millions, Hbg. 12.1 gm., W.B.C. 10,050, neutrophils 57 per cent, basophils 1 per cent, lymphocytes 31 per cent and monocytes 11 per cent. The urine and spinal fluid were negative. The basal metabolic rate ranged between 10 and 36 per cent above standard.

At this time a diagnosis of myasthenia gravis, hyperthyroidism and rheumatic valvular heart disease was made.

Course: Following admission to hospital in *February 1929*, the patient complained of marked weakness of the extremities and trunk. Breathing was difficult. She remained in hospital for approximately six months and was treated with adrenal cortical extract with little or no improvement.

Second Admission, October 1930: At this time the physical examination revealed no change from her previous examination. The basal metabolic rate varied between 15 and 36 per cent above standard. She was discharged in November 1930, her condition being unchanged. Following this the patient was given roentgen ray irradiation therapy over the thyroid gland. She was not seen again until June 1933 at which time it was noted that the basal metabolic rate was 2 per cent below standard and her strength was somewhat improved although the eye signs persisted.

Third Admission, September 1937: At this time she was readmitted for prostigmine therapy, the drug being given both intramuscularly and orally for a period of six weeks. This treatment was associated with considerable improvement. However, treatment was discontinued because of the occurrence of diarrhea and increased menstrual flow. She was discharged, her condition remaining essentially unchanged.

Fourth Admission, July 1938: The patient entered hospital because of an exacerbation of her symptoms. Five weeks prior to this admission she had noticed increased nervousness, tremor of hands, profuse sweating, palpitation and a ravenous appetite. She had lost weight despite her increased food consumption. She complained particularly of marked weakness in her arms. At this time she was so weak that she was unable to walk without assistance.

Physical examination revealed findings similar to those noted on her first admission. The temperature was 100.8°F., pulse 116, respirations 20, and blood pressure 135/75 mm. of Hg. She was thin and very nervous in appearance. Many choreiform movements were observed. There was exophthalmos of a moderate degree, bilateral ptosis and ophthalmoplegia. The visual fields were markedly limited above. The thyroid was definitely enlarged, but no bruit could be heard over the gland. Examination of the heart revealed tachycardia and signs compatible with mitral stenosis. The skeletal muscles were particularly weak and there was a coarse tremor of the extended fingers.

The laboratory data at this time were as follows: R.B.C. 4.24 mil-

lions, Hgb. 12.2 gm., W.B.C. 6,500 with a normal differential count. The blood non-protein nitrogen was 29 mg., the blood sugar 86 mg., serum calcium 11.1 mg., inorganic phosphorus 4.0 mg., and cholesterol 192 mg. per 100 cc. The serum protein was 6.7 gm. per 100 cc. The basal metabolic rate was 46 per cent above standard. An electrocardiogram revealed a rate of 100; the rhythm was sino-auricular, the P.R. interval 0.17 sec., and the Q.R.S. complex 0.06 sec. The T-waves were upright.

Course in Hospital: She was given combined prostigmine and guanidine hydrochloride therapy with only temporary improvement. The prostigmine was continued orally in doses of 15 mg. four times daily. On this regimen the spontaneous urinary creatine excretion approximated 420 mg. per day (creatine-free diet). Following the administration of an oral dose of 2.64 gm. of creatine, a total of 47 per cent was excreted (Normal excretion less than 30 per cent) (Chart 1). The basal metabolic rate fluctuated between 28 and 35 per cent above standard. After preliminary studies had been completed, treatment with Lugol's solution (1 cc. 3 × daily) was begun. Following the institution of treatment with Lugol's solution, the creatine excretion fell abruptly to approximately 50 mg. per day and only 28 per cent of the oral dose of 2.64 gm. of creatine was excreted as compared to 47 per cent prior to iodine therapy. The basal metabolic rate decreased slightly during this period, and the patient's general condition improved. Twenty-five days after treatment with Lugol's solution had been instituted, a subtotal thyroidectomy was performed successfully under cyclopropane anesthesia.

General improvement followed subtotal thyroidectomy but the ptosis and ophthalmoplegia did not change appreciably. The patient gained in strength and was soon able to walk despite the fact that prostigmine therapy had been discontinued temporarily. At this time the spontaneous daily excretion of creatine was less than 100 mg. per day (creatine-free diet). An oral dose of creatine (2.64 gm.) given at this time was followed by only 19 per cent excretion. She was now able by forceful expiration to raise the mercury in a manometer to a new high mark (Chart 1). After the injection of 1.5 mg. of prostigmine intramuscularly, the patient was not able to increase this reading. However, prostigmine therapy now resulted in the complete

disappearance of the ptosis during the period of action of the drug. The ophthalmoplegia was also improved greatly during prostigmine treatment.

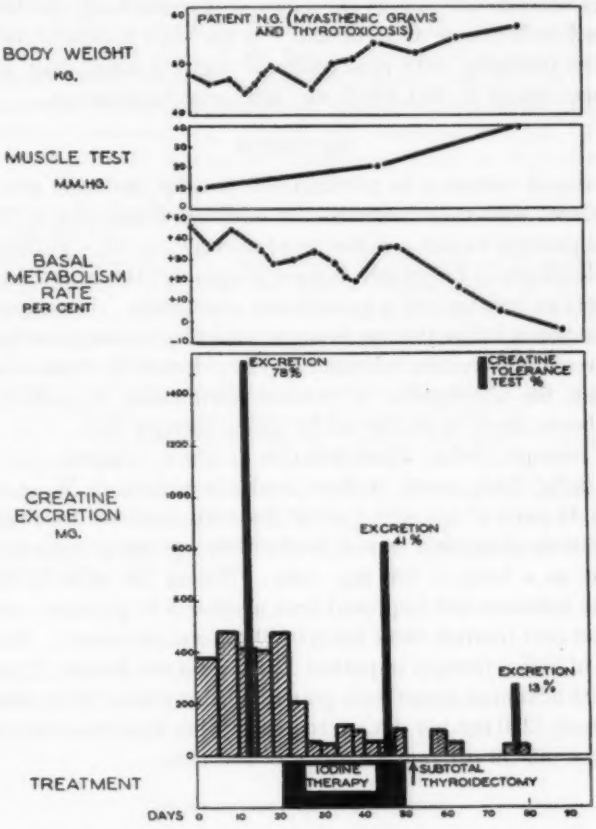

CHART 1. EFFECT OF IODINE THERAPY ON CREATINE EXCRETION IN PATIENT N. G. (MYASTHENIA GRAVIS AND THYROTOXICOSIS)

Six weeks after subtotal thyroidectomy, she was discharged from the hospital. At this time she was able to walk, but fatigued readily. The ptosis and ophthalmoplegia persisted. Treatment with the same dose of prostigmine which had been given prior to operation was now

resumed. This was associated with further improvement in strength and marked improvement in the eye signs. During the past two years she has been able to resume her regular occupation as a public school teacher whereas previous to the subtotal thyroidectomy she had been confined to her home as an invalid. It has been necessary for her to continue treatment with prostigmine 15 mg. 2–4 times daily which is the same dosage as that which was used prior to operation.

DISCUSSION

Decreased tolerance to administered creatine occurs in practically all patients with thyrotoxicosis. In addition, a majority of the thyrotoxic patients excrete creatine spontaneously (9, 10). Patients with myasthenia gravis frequently, but not invariably (11), have a decreased tolerance to creatine and a spontaneous creatinuria. In patients with thyrotoxicosis, iodine therapy is accompanied by a prompt and striking improvement in creatine tolerance and by a decreased creatinuria. In contrast, the abnormality in creatine metabolism in patients with myasthenia gravis is unaffected by iodine therapy (11).

For example, iodine administration (Lugol's solution, 1 cc. three times daily) for a period of three weeks in patient A. W., a colored female 34 years of age with typical thyrotoxicosis, was followed by a reduction in creatinuria from a level of 800 mg. daily, prior to iodine therapy to a level of 100 mg. daily. During the same period the creatine tolerance test improved from a value of 67 per cent to a value of 18 per cent (normal value being 0–30 per cent excretion). A similar period of iodine therapy in patient L. K., a colored female, 22 years of age, with advanced myasthenia gravis, failed to reduce the spontaneous creatinuria (250 mg. per day) or to improve the impairment in creatine tolerance (45–50 per cent excretion of test dose).

SUMMARY AND CONCLUSIONS

The coexistence of myasthenia gravis and thyrotoxicosis in a young, colored female is reported and the improvement in muscular function which followed subtotal thyroidectomy is described. A study of the effect of iodine therapy on creatine metabolism was found to be extremely helpful in establishing the extent to which the disorder in thyroid function aggravated the symptoms of myasthenia gravis.

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A RIBOFLAVIN EXCRETION TEST AS A MEASURE OF RIBOFLAVIN DEFICIENCY IN MAN

VICTOR A. NAJJAR AND L. EMMETT HOLT, JR.

From the Harriet Lane Home, The Johns Hopkins Hospital, and the School of Medicine, The Johns Hopkins University

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It is well recognized that a deficiency of riboflavin in the diet is reflected in a diminished urinary excretion of flavin. Such low flavin excretions have been observed in experimental animals fed diets poor in riboflavin (1, 2, 3), in human ariboflavinosis (4, 5) and in normal human subjects (6, 7), whose intake of riboflavin was restricted. Although most instances of symptomatic ariboflavinosis have been associated with a twenty-four hour flavin excretion well below the normal average, it has not been possible to define a level of twenty-four hour flavin excretion characteristic of riboflavin deficiency, since the urinary flavin output varies with the immediate intake and gives no indication as to the state of the body stores of this vitamin. An experiment which we performed on a volunteer subject illustrates this point clearly.

The subject, a male adult of 26 years, subjected himself for 30 days to a diet of purified casein, butter, boiled rice and water—a diet entirely free of riboflavin. The daily output of flavin in the urine was measured, and is given in the accompanying table (Table 1). It will be observed that the flavin excretion fell to zero on the sixteenth day of this regime, and, despite the fact that the diet was continued without alteration for another two weeks, no symptoms of ariboflavinosis developed. It is thus apparent that complete absence of riboflavin in the urine does not necessarily indicate the presence of ariboflavinosis, and, conversely, ariboflavinosis has been observed to develop (5) when the twenty-four hour urine specimen contained from 24 to 119 micrograms of flavin. It therefore becomes necessary to find a more accurate laboratory test for the presence of this condition.

The possibility that an excretion test, similar to those employed

with success in ascorbic acid deficiency and in thiamin deficiency, might prove of value in the diagnosis of riboflavin deficiency at once suggested itself. A few observations with such excretion tests have already been made by others. Neuweiler (8) reported that an infant with suspected ariboflavinosis completely retained a large dose of riboflavin. Axelrod, Lipton and Elvehjem (3) studied dogs with riboflavin deficiency after oral and subcutaneous administration of the vitamin and reported that these animals retained a high percentage of

TABLE 1

Daily Excretion of Riboflavin in Urine of an Adult on Riboflavin-Free Diet

DAY OF EXPERIMENTAL DIET	RIBOFLAVIN IN URINE
	micrograms per 24 hours
1	135
2	80
3	73
4	61
5	83
6	75
7	28
8	13
9	—
10	18
11	45
12	55
13	53
14	12
15	—
16	0
17–30	0

the administered dose, in contrast to the normal dog. On the other hand, Axelrod, Spies, Elvehjem and Axelrod (9) working with deficient human subjects, reported that the riboflavin "saturation" test had little diagnostic value; their findings in patients with riboflavin deficiency differed little from those obtained in normal subjects. Klein and Kohn (11) administered large doses of riboflavin orally to two human subjects and observed increased excretion of riboflavin in the urine as a result of "saturation" of the tissues. They did not study deficient individuals.

Our own studies, carried out with a somewhat different technique

from that employed in the above mentioned studies, are reported herewith. As a standard riboflavin excretion test we employed an intravenous injection of 1 mg. of riboflavin[1] dissolved in distilled water. The tests were carried out after an overnight fast. Before the injection, urine was collected for a control period of one hour. Following the injection the excretion in the urine was followed for half-hourly and then for hourly periods for four hours. Measurements of riboflavin were made by the fluorometric method of Najjar (10).

The results of excretion curves made in ten normal subjects and in four subjects with ariboflavinosis[2] are shown in Table 2. It will be seen that a marked excretion of riboflavin occurs during the first half hour following the injection. During the second hour and during subsequent hours the excretion falls off rapidly, approaching that of the initial control period at the end of that time. From 32 to 72 per cent of the injected dose is retained in the body.

In contrast to these findings are riboflavin excretion curves on four subjects with induced riboflavin deficiency. In these subjects the excretion of riboflavin in the urine is strikingly less, from 81 to 93 per cent of the injected dose being retained during the four-hour test period. It would seem that in cases of ariboflavinosis more than 80 per cent of a test injection of 1 mg. is not recoverable from the urine in the succeeding four hours, indicating a greater retention of this vitamin than occurs in the normal subject.

The data in the table suggest further that the excretion of such a test dose of riboflavin is influenced by the weight of the subject—the lighter normal subjects tending to excrete more of the test dose than the heavier ones. It is probable that if the test injection had been based on the weight of the subject, the variations seen in the group of normal subjects would have been considerably reduced. In the future

[1] Most of these tests were carried out with a soluble preparation of riboflavin ("flavaxin") supplied by the Winthrop Chemical Company, to whom we are indebted for this material. We have made parallel tests on the same individual, using this preparation as well as a standard (Merck) product, and have obtained identical results.

[2] For the opportunity of studying these patients we are indebted to Dr. W. H. Sebrell and Dr. R. E. Butler of the Nutrition Laboratory of the National Institute of Health, Washington, D. C., to whom we wish to express our appreciation.

it would seem preferable to employ a test dose of 0.016 mg. per kilo rather than a flat dose of 1 mg. for all subjects.

TABLE 2

Riboflavin Excretion Tests in Normal Subjects and Subjects with Ariboflavinosis

Figures represent micrograms in urine after intravenous injection of 1 mg.

SUBJECT	SEX	WEIGHT	CONTROL PERIOD, 1 HOUR BEFORE TEST	EXCRETION AFTER TEST INJECTION					
				First half hour	Second half hour	Second hour	Third hour	Fourth hour	Total 4 hours
Normal subjects									
		kgm.							
Za	M	73	—	210	25	20	22	20	297
Fr	F	67	16	228	16	16	9	8	277
Gr	F	62	11	156	40	17	48	24	285
Na	M	62	12	232	27	25	27	20	331
We	M	60	—						354
Br	M	60	33	292	56	55	42	21	466
Le	F	56	49	317	123	84	80	79	683
Sc	F	55	7	243	11	18	9	6	287
Zi	F	53	25	330	43	65	51	40	529
Cl	F	46	6	284	41	30	31	35	421
Subjects with ariboflavinosis*									
No. 40	F	48	1	37	17	5	10	5	74
No. 51	F	45	5	159	16	4	2	2	183
No. 71	F	64	4	166	7	9	8	4	194
No. 27	F	82	—	144	11	3	1	tr	159

* Protocols of these subjects are given below:

Subject No. 40. Age 52. At the time of the test showed grayness at the angles of the lips, nasal discharge and ulceration on right nasal vestibule.

Subject No. 51. At the time of the test showed grayness at the angles of the lips, denudation of the lower lip at the point of contact, marginal inflammation of the gums, increase in sebaceous deposits at the nasolabial folds and fissuring of the left vestibule of the nose.

Subject No. 71. At the time of the test exhibited grayness in the angles of both lips, denudation of both nasolabial folds, smooth tongue and increase in sebaceous deposits in the nasolabial folds.

Subject No. 27. At the time of the test the only symptom was a fissure with slight maceration at the right angle of the lips.

It would appear then that the riboflavin excretion test, when suitably carried out, is an index of a deficient store of this vitamin, a more valuable index than the twenty-four hour excretion of riboflavin in the

urine. On comparing our results with those reported by Axelrod and his collaborators (9) it may be noted that these investigators, who concluded that the excretion test in man was of little value, used intravenous doses 10 to 20 times as large as those employed by us. It seems likely that such large doses may have so far exceeded the quantity that could be utilized even by a deficient individual as to leave a great excess available for urinary excretion; consequently the anticipated low excretion after the injection did not occur. The quantity of riboflavin administered by them was so great that maximal excretion continued well beyond the first half-hour period, in one instance for a full three hours. The ability of the kidneys to excrete the flavin may well have been the factor determining the quantity excreted under these circumstances.

SUMMARY

1. The twenty-four hour output of flavin in the urine is not an accurate measure of riboflavin deficiency, since it reflects only the immediate dietary intake.

2. A riboflavin excretion test has been studied which appears to correlate more closely with clinical riboflavin deficiency.

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POISON IVY DERMATITIS

I. The Diagnostic Value of the Patch Test Made with an Ether Extract from Fresh Leaves and Stems of the Poison Ivy Plant

EDMUND L. KEENEY, STEWART SUNDAY, LESLIE N. GAY AND KENNETH LYNCH

From the Protein Clinic, Department of Medicine, The Johns Hopkins School of Medicine and Hospital

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The "patch" test technique provides a suitable method of testing for hypersensitivity in the human to the poison ivy plant. Because the specific sensitizing substance in the sap of the poison ivy plant has never been chemically isolated, it has been impossible to standardize the technique of patch testing for hypersensitivity to the plant.

The sensitizing substance in the sap of the poison ivy plant is soluble in fat solvents and can be extracted from the plant with alcohol, acetone, benzin, toluene and ether. There is variation amongst investigators as to methods of extracting and as to substances employed in the process of extracting. Before it is possible to study thoroughly hypersensitivity in the human to the poison ivy plant, it is necessary to determine the efficiency of the extract employed in the experiments. First a potent extract must be found, and secondly a suitable dilution of this extract must be made so that the reactions obtained are well coordinated with the clinical data. In other words, the dilution must be strong enough to elicit true hypersensitivity but not so strong as to give false positive reactions. The purpose of this paper is to establish the reliability of a 1:25 peanut oil dilution of an ether extract of the fresh leaves and stems of the poison ivy plant as prepared by the late Dr. A. H. W. Caulfeild (1, 2) in determining hypersensitivity in humans.

The technique of patch testing is simple (Fig. 1). A small amount of the extract is applied on the volar surface of the forearm with a glass rod measuring 2 mm. in diameter. Cotton is placed over the site where the extract has been applied and the "patch" is then placed over

the cotton. The patches are removed 7 days (3) after the test is made and the results are noted. Patch tests are recorded as positive when obvious erythema or erythema with vesiculation occurs. All doubtful reactions are classified as negative.

FIG. 1. The technic of patch testing: A. The extract is applied with a rod 2 mm. in diameter. B. The area is covered with a small piece of cotton. C. The "patch" is applied. (This illustration first appeared in *The Journal of the Indiana State Medical Association* and is here reproduced with the permission of the editor of that journal.)

Patch tests were performed on 468 individuals, of whom 139 were male medical students varying in age from 20 to 27 years and of whom 329 were male employees of Baltimore City varying in age from 20 to 67 years. Sixty-seven (48 per cent) of the 139 medical students, and 142 (44 per cent) of the City employees gave positive histories of poison ivy dermatitis. Of the entire 468 individuals studied, 44.6 per cent gave positive histories. One hundred and forty-seven (70 per cent)

of the 209 individuals that gave positive histories reacted with a positive patch test (Table I).

An attempt was made to grade the degree of hypersensitivity to the poison ivy plant in 92 of the individuals that gave positive reactions. Those individuals giving reactions measuring less than 1.0 × 1.0 cm. were classified as Grade I sensitivity; those individuals with reactions greater than 1.0× 1.0 cm. but less than 2.0 × 2.0 cm. were classified

TABLE I

Results of Patch Tests for Poison Ivy Hypersensitivity on 468 Men

NUMBER WITH POSITIVE HISTORIES OF POISON IVY DERMATITIS	NUMBER WITH POSITIVE HISTORIES AND POSITIVE PATCH TEST REACTIONS	NUMBER WITH NEGATIVE HISTORIES OF POISON IVY DERMATITIS	NUMBER WITH NEGATIVE HISTORIES AND POSITIVE PATCH TEST REACTIONS
209	147 (70%)	259	37 (14%)

TABLE II

Classification of Poison Ivy Hypersensitivity in 111 Individuals

GRADE OF THE POSITIVE PATCH TEST REACTION*	NUMBER WITH POSITIVE HISTORIES AND POSITIVE PATCH TEST REACTIONS	NUMBER WITH NEGATIVE HISTORIES AND POSITIVE PATCH TEST REACTIONS
Grade I	12 (13%)	5 (26%)
Grade II	41 (44%)	8 (42%)
Grade III	39 (43%)	6 (32%)

* Grade I signifies reactions less than 1.0 x 1.0 cm.; Grade II signifies reactions greater than 1.0 x 1.0 cm. but less than 2.0 x 2.0 cm.; Grade III signifies reactions greater than 2.0 x 2.0 cm.

as Grade II sensitivity; and those individuals with reactions greater than 2.0 × 2.0 were classified as Grade III sensitivity (Table II).

Thirty-seven (14 per cent) of the 259 individuals giving negative histories of poison ivy dermatitis, gave positive patch tests (Table I). Nineteen of the 37 positive reactions were classified according to their respective grade of sensitivity (Table II).

It has been concluded from these results that a 1:25 peanut oil dilution of an ether extract of the fresh leaves and stems of the poison ivy plant is a reliable substance for determining human hypersensitivity to the poison ivy plant.

SUMMARY

1. Two hundred and nine (44.6 per cent) of 468 male individuals chosen at random and ranging in age from 20 to 67 years, gave positive histories for poison ivy dermatitis.

2. One hundred and forty-seven (70 per cent) of the 209 individuals giving positive histories of poison ivy dermatitis, gave positive patch test reactions to a 1:25 peanut oil dilution of an ether extract prepared from the fresh leaves and stems of the poison ivy plant.

3. Thirty-seven, or 14 per cent, of the 259 individuals that gave negative histories of poison ivy dermatitis gave positive reactions to the 1:25 dilution of the ether extract.

4. The positive patch test reactions of 92 individuals with positive histories of poison ivy dermatitis were classified into grades of sensitivity. Thirteen per cent were classified as Grade I sensitivity (reactions less than 1.0 × 1.0 cm.); 44 per cent as Grade II sensitivity (reactions greater than 1.0 × 1.0 cm., but less than 2.0 × 2.0 cm.); and 42 per cent as Grade III sensitivity (reactions greater than 2.0 × 2.0 cm.).

5. Nineteen of the 37 individuals giving negative histories of poison ivy dermatitis, but positive patch test reactions were classified into grades of sensitivity. Twenty-six per cent were classified as Grade I sensitivity; 42 per cent as Grade II sensitivity; and 32 per cent as Grade III sensitivity.

6. It is concluded that patch tests performed with a 1:25 peanut oil dilution of an ether extract of the fresh leaves and the stems of the poison ivy plant accurately reveal hypersensitivity in the human to the poison ivy plant. The chances of eliciting false positive reactions with this extract are slight.

We wish to acknowledge with gratitude the coöperation of Mr. Elmer F. Bernhardt, Chief of Central Pay Roll Bureau and Director of Disability Compensation Division of City of Baltimore, and his staff.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Cardiac Classics. A Collection of Classic Works on the Heart and Circulation with Comprehensive Biographic Accounts of the Authors. Fifty-Two Contributions by Fifty-One Authors. By FREDRICK A. WILLIUS and THOMAS E. KEYS. 858 pp. Illus. $10.00. *C. V. Mosby Company, St. Louis, 1941.*

This book may safely be hailed as a standard history of cardiology. Selected readings from the anatomy, physiology and clinical observations relating to diseases of the heart are combined with brief accounts of the lives of the fathers of this subject. Some readers of such a book will always wish that a little more credit had been given their personal medical heroes. Thus, the reviewer would be pleased if the next edition should give Dr. James Hope some recognition for his remarkable work on experimental aortic insufficiency and his systematic elucidation of cardiac murmurs. Also, in addition to his other discoveries, Morgagni may be credited with a brief first description of coarctation of the aorta.

The authors are to be congratulated on making available to the profession a mass of material that would require enormous perseverance on the part of most of us to ferret out. The student of the subject can not afford to be without this volume.

J. T. K.

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN. 2nd ed. 468 pp. Illus. $5.00. *C. V. Mosby Company, St. Louis, 1941.*

The title and manufacture of this volume, suggesting a *vade mecum*, are deceptive. Actually, it is a first-class text-book of the subject indicated. Though it slips into a pocket it contains 450 pages of excellent paper, with many suitable illustrations. One may dissent from some of the views presented, such as the functional theory of hypertension (p. 32); the use of digitalis in hyperthyroid states; and the exhibition of as much as three grains of thyroid extract daily in myxedema. However, the author's opinions are carefully and modestly put forward, and the book may be highly recommended.

J. T. K.

Medical Diagnosis and Symptomatology. By SAMUEL A. LOEWENBERG. 5th ed. 1139 pp. Illus. $12.00. *F. A. Davis Company, Philadelphia, 1941.*

An unusually comprehensive summary of diagnostic procedures, the present volume of 1059 pages contains new chapters on Vitamins and Geriatrics. The

material relating to Cardiovascular Diseases, Endocrinology and Blood has been revised or re-written. Cardiac hypertrophy is given as an early sign of coarctation of the aorta; this is contrary to general observation, except in cases complicated by aortic insufficiency. The illustrations are excellent. There is a very complete index.

J. T. K.

Brucellosis (Undulant Fever). By HAROLD J. HARRIS. 286 pp. Illus. $5.50. *Paul B. Hoeber, New York & London, 1941.*

This book is extremely interesting reading. It is definitely on the propaganda side to make physicians brucellosis conscious, but the evidence offered as to the widespread nature of this disease is not too conclusive.

E. L. B.

Human Nature in the Light of Psychopathology. By KURT GOLDSTEIN. 258 pp. $2.50. *Harvard University Press, Cambridge, Mass., 1940.*

This, to my mind, is one of the great books of recent medical literature. It contains the William James Lectures given at Harvard University in 1937–38 by Dr. Goldstein. What he gives us is his summing up of his philosophy as to the nature of human personality. There is a rather difficult first chapter, then, using as a springboard the observation of the disturbances of behavior following frontal lobe damage, Dr. Goldstein proceeds to develop a holistic conception of man's neurological as well as personality integration, pointing out that the analytic approach of science can never hope to do justice to the multiplicity of functions inherent in the total human organism. What happens when this unique balance is upset by disturbance at any level of integration is seen in terms of catastrophe, resulting in the diffuse experience of anxiety, the more topically determined experience of fear. The nature of adaptation is searchingly scrutinized and there is a provocative discussion of the role of reflex, instinct, and drive; all three of which, having been given undue emphasis in the past, have led to isolated and sterile schools of psychology. His suggestion for a true understanding of personality variables lies in his emphasis of preferred performance, and the right of every individual to work out his own self-actuation. Man's relation to the social group is the material of the final two chapters—chapters that illuminate the very essence of the present social debacle.

There is great wisdom in this book, and the vision to see beyond schools and specialties. What one welcomes most is the restoration of human spontaneity into academic thought. Dr. Goldstein finds serious flaws in the psychoanalytic emphasis on past experience as the conditioner of all adult behavior responses. What he stands for has much in common with the Meyerian determination to work with all the factors, past and present, which enter into the balance between self, others, and the environment.

I cannot recommend this book too highly. It is thoughtful and wise; a real answer to all those specialists who view man from their arbitrary and isolated,

often allegorical and speculative, laboratories and armchairs. It is good to have so brilliant a statement of a point of view slowly but certainly emerging in medical thought of today: the necessity to put aside the accumulated minutiae of analytic procedures for a broad view of the total organismal synthesis.

And finally, there is a beautiful review of the pertinent literature. This book should be obligatory for all students of human behavior.

T. A. C. R.

The Mask of Sanity. By HERVEY CLECKLEY. 298 pp. $3.00. *C. V. Mosby Company, St. Louis, 1941.*

This book combines a very real and valuable psychiatric discussion with the style and persuasiveness of a novel. The author presents a series of cases illustrative of a group of so-called psychopathic personalities. He then contrasts this with other types of psychiatric disorders and other groups of personality disturbances. Finally he draws a composite picture of the psychopath as he sees him, and concludes the book with a somewhat speculative discussion of the nature of the disorder and some tentative proposals for its management.

The weakest part of the book is in the presentation of the rather full and extremely interesting case examples. Unfortunately he has chosen as types a group in which the individuals are remarkably alike, and in which the factor of alcoholism is a leading one. It is a pity that the case histories are not more representative of the total problem. Those presented are convincing enough, largely by their reiterative similarity. The review of the literature on the subject is excellent, and points out the lacks in classification, in interpretation, and even in appreciation of the essential nature of the psychopath. There has been, as the author points out, a great dearth of interpretive studies.

In the final chapters, the author presents his own interpretation, admittedly speculative, and asks that we give up our speculation of "sane" versus "insane" in favor of a view of the disorder as "semantic dementia," brought about by long-standing habit formation along unorthodox and distorted pathways.

This book makes for fascinating reading because of its fluent style, its broad familiarity with life, letters, and psychiatric literature. The book is recommended heartily, although its final value as a textbook is marred somewhat by its limited choice of case material, the speculative character of some of the reasoning, and occasional reiterativeness. It is eminently worth while, however, both to the layman and to the specialist, and should be welcomed as one of the outstanding contributions to the study of this long-neglected group of disturbances.

T. A. C. R.

Introduction to Dermatology. By RICHARD L. SUTTON and RICHARD L. SUTTON, JR. 4th ed. 904 pp. Illus. $9.00. *C. V. Mosby Company, St. Louis, 1941.*

This text book intended for undergraduate and postgraduate teaching, in keeping with expanding knowledge in the field of dermatology, has attained to large volume size. Although it is about one-half the size of the last edition of

the standard volume on skin diseases by these authors, it is comprehensive and complete in its treatment of the subject matter. Much space is saved by the frequent interspersion of paragraphs in small print. Many data are assembled in outline form which contributes to clarity and completeness.

No aspect of dermatology is neglected. Thorough and very readable chapters are presented under captions which should be inviting to the curious in any field of medicine: Metabolic Dermatoses, Atrophies, Neuroses, Pigmentations and Depigmentations, Malformations, New Growths, Virus Diseases, Rickettsial Diseases, Diseases due to Bacteria, Fungi, Protozoa, Metazoa, Diseases of Mucosae Adjoining the Skin, etc.

The authors amply discuss and evaluate the recent contributions to dermatology. Their unstinting expression of personal opinions makes not only interesting reading, but should add to the profit, particularly in the domain of therapy, to be derived by the reader who seeks something more than handbook glimpses of the subject. The use of a low fat diet and thyroid extract in acne vulgaris is advocated on the basis of a concept of this disease which appears logical and at least is enlightening.

The illustrations, both clinical and histological are adequate and very good. Much space is saved in the text by placing a well-chosen extensive bibliography at the back of the book.

The book is an excellent introduction to dermatology and, as the authors say, it sufficiently outlines the scope of the speciality beyond provincial boundaries. For these reasons the conscientious student deserves a copy and the postgraduate student and practitioner will profit from the easy manner in which it will bring them abreast of the latest advances in this field of medicine.

M. H. G.

Scabies—Civil and Military. By REUBEN FRIEDMAN. 288 pp. $3.00. *Froben Press, New York, 1941.*

The author has already proved himself an outstanding student of the subject and his unabated interest in the Acarus scabiei and its exploits has produced this book which would profit every physician practically and culturally to read in his leisure. In the discussion of this disease—in civil and military life—with many full, apt and often amusing quotations from the classical literature, many points in diagnosis and in differential diagnosis (particularly from pediculosis corporis) are given. In military life scabies evidently shows a greater predilection for the penis and less for the hands and fingers than in civil life and the soldier is particularly prone to coccogenous complications and so-called inflammation connective tissue (I.C.T.).

The author believes there is no absolute immunity to scabies. Some individuals seemingly do not react at all to the presence of the itch mite and some, although bearing objective evidence of the disease are symptomless. There are, therefore, scabies carriers and all contacts should be examined or/and treated.

That the incidence of scabies varies widely in different parts of the United

States is well illustrated in a chart compiled from figures collected from a substantial number of hospitals throughout the country. The effect of immigration on the increase of the disease at the turn of the century was decisive. Scabies is one of the great military diseases and the story of the role which the itch mite played in the "military might" of various countries when at peace and at war is a tribute to the zealous research of the author. War entails crowding and lack of personal cleanliness because of infrequent washing and change of clothing. The result is a scabies scourge which by furlough and demobilization, is reflected in pronounced war and post-war increase of incidence in the civil population.

The history of the therapy of scabies is a chapter of absorbing interest. After centuries of blind devotion to the teaching of Galen that internal treatment for this disease was more important than external treatment, the medical profession was unable to appreciate the epochal discovery of the causative animalcule by Bonomo in 1687. Interestingly enough, however, the victims of scabies were relieved of their suffering by self-applied local therapy and from their money by quacks who provided it. The amazing tendency to "theoretical pedantry" rather than to the observation of facts, and blind adherence to the traditions of an "archaic past" are well brought out by the fact that even with the rediscovery of the itch mite by Renucci, in 1834, there were still many skeptics among physicians. However, "with the publication, in 1844, of Hebra's classic treatise, *Ueber Krätze*, it may be said that the most conclusive, if not the concluding, chapter on the theretofore debated question of the etiology and treatment of scabies had finally been written".

The final chapters in the book on the treatment of scabies, not only exhaustively discuss all past and present forms of treatment of scabies but present details as to the chemical structure, rationale, and technique of application of the various agents employed. The author is in agreement with "numerous other authorities" that sulphur ointment is the treatment of choice.

The appended index is excellent by all criteria.

M. H. G.

BOOKS RECEIVED FOR REVIEW

Collected Papers of the Mayo Clinic and the Mayo Foundation. Edited by RICHARD M. HEWITT [and others]. Volume 32, 1940. 1190 pp. Illus. $11.50. *W. B. Saunders Company, Philadelphia and London, 1941.*

Asclepian Ramble. A reprint of Chapter I of Volume IV, Part 1 of "The Patient and the Weather" by W. F. PETERSEN and M. E. MILLIKEN. 106 pp. *Edwards Brothers, Ann Arbor, Michigan.*

Kidney Disease. A reprint of Chapter VI of Volume IV, Part 1 of "The Patient and the Weather" by W. F. PETERSEN and M. E. MILLIKEN. Pp. 439–540. *Edwards Brothers, Ann Arbor, Michigan.*

Infantile Paralysis. A Symposium delivered at Vanderbilt University, April, 1941. 239 pp. Illus. $1.25. *National Foundation for Infantile Paralysis, New York, 1941.*

Papers of Wade Hampton Frost, M.D. Edited by KENNETH F. MAXCY. 628 pp. $3.00. *The Commonwealth Fund, New York, and Humphrey Milford, Oxford University Press, London, 1941.*

Abdominal Surgery of Infancy and Childhood. By WILLIAM E. LADD and ROBERT E. GROSS. 455 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

Lymphatics, Lymph, and Lymphoid Tissue. By CECIL KENT DRINKER and JOSEPH MENDEL YOFFEY. 406 pp. Illus. $4.00. *Harvard University Press, Cambridge, Mass., 1941.*

Out of the Test Tube. By HARRY N. HOLMES. 3rd ed. 305 pp. Illus. $3.00. *Emerson Books, New York, 1941.*

Principles of Microbiology. By FRANCIS E. COLIEN and ETHEL J. ODEGARD. 444 pp. Illus. $3.00. *C. V. Mosby Company, St. Louis, 1941.*

Principal Nervous Pathways. By ANDREW THEODORE RASMUSSEN. 2nd ed. 73 pp. Illus. $2.50. *The Macmillan Company, New York, 1941.*

Necropsy. By BÉLA HALPERT. 75 pp. $1.50. *C. V. Mosby Company, St. Louis, 1941.*

Clinical Immunology, Biotherapy and Chemotherapy. By JOHN A. KOLMER and LOUIS TUFT. 941 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

Essentials of Pharmacology and Materia Medica for Nurses. By ALBERT J. GILBERT and SELMA MOODY. 251 pp. Illus. $2.25. *C. V. Mosby Company, St. Louis, 1941.*

Text-Book of Bacteriology. By R. W. FAIRBROTHER. 3rd ed. 451 pp. Illus. $5.00. *C. V. Mosby Company, St. Louis, 1941.*

Essentials of Electrocardiography. By RICHARD ASHMAN and EDGAR HULL. 2nd ed. 373 pp. Illus. $5.00. *The Macmillan Company, New York, 1941.*

Early Treatment of War Wounds. By WILLIAM ANDERSON. 96 pp. Illus. $1.50. *Oxford University Press, London: Humphrey Milford, 1941.*

Roentgen Technique. By CLYDE MCNEILL. 2nd ed. 329 pp. Illus. $5.00. *Charles C. Thomas, Springfield, Illinois, 1941.*